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Some Cytochemical and Cytologic Features of Senile Keratosis

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BIOPSIES OF SENILE KERATOTIC LESIONS FROM 8 PATIENTS WERE SUBJECTED TO HISTOLOGIC AND CYTOCHEMICAL EXAMINATION BY DR. COWDRY AND DR. ANDREW. THE DIVERSITY WITHIN THESE IMPORTANT PRECANCEROUS LESIONS IS EMPHASIZED AND THOROUGHLY DISCUSSED. THIS PAPER WAS GIVEN AT THE SECOND ANNUAL SCIENTIFIC MEETING OF THE GERONTOLOGICAL SOCIETY IN CHICAGO, NOVEMBER 5-6, 1949.

SENILE keratosis is a lesion which appears with considerable frequency in old age. The plaques are multiple and the usual site is on the exposed surface of the body, particularly on the face and on the backs of the hands. Senile keratosis is a definitely precancerous lesion in that epithelioma often takes origin in a plaque. The multiple nature of the lesions would seem to increase the chances of malignant change.

In spite of its frequent occurrence and its precancerous nature, relatively few investigations on senile keratosis have been undertaken. Gans (10) pointed out how very few accounts of this lesion are to be found in the German literature prior to publication of his handbook. Only two authors, Jadassohn (14) and Freudenthal (9) had distinguished senile keratosis from verruca senilis, a very different type of lesion. Gans says that plaques of senile keratosis, while they tend to grow larger and more numerous, may remain unchanged for very long periods and may even show spontaneous regression. Such plaques are, of course, not precancerous.

Montgomery and Dorffel (20) distinguished clearly between senile keratosis and verruca senilis. The latter, they say, very seldom becomes carcinomatous and then only after trauma or chronic irritation. The former is a truly precancerous lesion, frequently undergoing apparently spontaneous transition to an epithelioma.

Montgomery (18) points out that individual plaques of senile keratosis may come to show all of the microscopic features of Bowen's disease, or carcinoma *in situ*. Bowen's disease itself, however, may persist as such without becoming invasive for as much as 6 to 30 years (Montgomery, 19).

Henschen (13) has obtained evidence that senile keratosis of the palms and soles may be caused to regress by treatment of the patient with androgen (testosterone propionate). This indicates a possible and interesting relationship of the lesion to endocrine dysfunction in old age, but this subject is still an obscure one.

We now possess considerable data on the cytologic, chemical, and cytochemical changes which occur during the transition of normal epidermis to hyperplastic, precancerous epidermis and on to actual cancer under the experimental conditions of methylcholanthrene carcinogenesis in the mouse (Cowdry, 5). It seems very worth while to forward attempts being made to establish, wherever possible,

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comparison between such changes in mice and those which occur in man during "spontaneous" carcinogenesis. Previous contributions dealing specifically with human epidermis as part of this correlation include papers by Evans, Cowdry, and Nielson (8), Cowdry, Cooper, and Smith (6) on microscopic properties, Suntzeff and Carruthers (28), and Stowell and Cooper (26) on chemical properties.

Materials and Methods

Lesions for sectioning were obtained from 8 persons. Seven of these subjects ranged in age from 66 through 81 years. One subject was only 40 years old. All subjects were of the Caucasian race. The age and sex of the subjects, site from which the lesion was taken, and other pertinent data are as follows:

Subject	Age and Sex	Site of lesion
A4278	40♂	Side of nose
A4545	66♀	Cheek
A3636	70♂	Temple
A3374	72♂	Neck
A4009	73♀	Cheek
A3860	74♀	Forehead
89054	79♂	Cheek
67505	81♂	Cheek

In no case was there any clinical evidence of malignancy in the lesion chosen.

The material to be sectioned was fixed in the fluid recommended by Scott (23) for the best results with microincineration. This consists of 9 parts of absolute alcohol and 1 part of neutral formalin. Dehydration was completed by several changes of alcohol. The tissue was then passed into xylol, infiltrated, and embedded in paraffin.

Sections were cut at 5μ. These were mounted in such a way that those to be subjected to microincineration alternated with those to be stained with hematoxylin and eosin. Not only did these sections correspond to this extent, but the sections for microincineration were mounted face up so that a very close approximation with the adjacent face of the stained section could be made in any particular case. Four slides of sections for staining, generally with 5 sections each, and the same number of sections for microincineration, were mounted.

Some sections remaining after this procedure were used in the cytochemical test for ribonucleic acid and some for staining with orcein for demonstration of the elastic tissue in the dermis.

The test for ribonucleic acid was that described by Brachet, as carried out as by Stowell (25), in which ribonuclease is allowed to act on some sections but not on others, and the sections are then stained with Pappenheim's methyl green-pyronin.

In addition to the study of sections, whole mounts of epidermis were made from several specimens. In these cases the epidermis was separated from the dermis by immersing the specimen in ½ to 1 per cent acetic acid for twelve to twenty-four hours, in the ice-box, and then teasing free the epidermal layer. The epidermis was mounted in balsam.

Observations

The generally accepted histologic picture of senile keratosis is that of epidermal hyperplasia accompanied by hyperkeratosis. Weidman (28, p. 403) says of the keratin: "The excess is an accumulation secondary to epidermal hyperplasia."

While hyperplasia was the most conspicuous feature of the lesions in our series as viewed with low power (fig. 2), regions in these lesions which seem to represent a definite atrophy of the epidermis were found. In two specimens (A3636 and 89054) this feature was particularly noteworthy. In these specimens division of the epidermis into characteristic layers was not possible over wide areas. The stratum germinativum was represented only by several layers of flattened cells and immediately above it is a heavy cornified layer in which the cells have retained well defined nuclei (fig. 3). We seem to see here an increased degree of cornification, or at least an unusually thick layer of cornified cells which cannot be described simply as secondary to epidermal hyperplasia.

In all of the 8 specimens studied we found an accumulation of lymphoid cells in the dermis immediately underlying the region of epidermal change. The degree of compactness of this accumulation varied from one lesion to another. In A3374, from a 72 year old man, the accumulation was particularly heavy and we received the impression that we might be dealing not with a simple infiltration of lymphocytes and plasma cells but rather with the presence of organized lymphoid tissue, developing along with the epidermal change.

The cellular details of the lesions were of considerable interest. Previous descriptions of cellular changes in senile keratosis have generally been confined to listing of the presence of bizarre nuclei, hyperchromatism, and possible amitosis, along with mitosis, in the lesions. We, also, have observed marked variation in cytologic structure of the keratoses as well as some features not hitherto reported.

The greatest degree of variation occurred among the cells of the spinous layer. Here there may be considerable variations in size and appearance in adjacent cells. Figure 8 shows the great discrepancy in size which occurs.

Another feature often seen in the keratoses and not in adjoining normal epidermis is the presence of conspicuous perinuclear vacuoles (fig. 8).

Certain areas, particularly where hyperplasia is marked, showed an especially strong development of the epithelial fibrillae so that these became visible within the cells even in the hematoxylin and eosin preparations (fig. 9).

Mitoses were seen but are present only in small numbers, hardly ever more than one or two per section, even in the most hyperplastic lesions. All of those which we have found have appeared to be essentially normal. They occurred characteristically in the spinous rather than in the basal cell layer (fig. 10). Incidentally in normal mouse epidermis mitotic frequency was greater in the spinous than in the basal cells (Cowdry, Van Dyke, and Geren 7). In the keratotic lesions mitoses were present chiefly in the down growths of epidermis.

Of particular interest was the occurrence of nuclear fission without mitosis, leading to binucleated and even multinucleated cells.

Figures 4 to 7 show some features of this process. In senile keratoses amitotic nuclear division seems to begin with an internal division of the nucleus, a separation into individual "fields" which are divided from each other by

what seems to be an extremely delicate membrane. Each field contains a nucleolus (fig. 4). The separation becomes more marked and we see two discrete nuclei in one cell but in intimate apposition (fig. 5). A tendency of each nucleus to round up then leads to a greater degree of separation.

Whether cell division follows nuclear division and new cells are produced, or whether it leads always or usually to binucleate cells, is a problem very difficult to resolve in this material. Some binucleate cells probably are formed in this manner and others through nuclear division by mitosis. We have been unable to observe any constriction of the cell following amitotic nuclear fission.

Occasionally the nuclear division is a sort of budding, or vesicle formation, in which one large portion is seen in contact with several small portions, any one of which may or may not contain a nucleolus.

Further comment on the significance of these nonmitotic divisions of the nucleus will be made in the discussion.

The areas of hyperplastic epidermis exhibited a varying degree of distinctness of the basal cell layer. In much of the epidermis there was nothing which properly could be designated as such a layer, except by position, the lowermost cells being large and generally polyhedral as were the other layers. In the down growths, however, the layer was much better defined and here the basal cells were columnar. A striking difference between the normal and keratotic epidermis was the lack of pigment in the latter. The transition from one to the other was very sharp and occurred within the space of a few cells.

The epidermis in the keratotic lesion showed small, varying numbers of lymphocytes. No great degree of infiltration of epidermis in any of our specimens was seen, most of the wandering cells appeared to be lymphocytes. Those examined seemed to be essentially normal, without evidence of karyorrhexis or other degenerative process (fig. 10).

The presence of lymphocytes in normal human epidermis has been reported by Kondo (15) and in normal mouse epidermis by Andreasen (1). We have had access to a large number of biopsy specimens of normal human skin. In these a small percentage (1 to 4 per cent) of lymphocytes present in the epidermis was found in every case. In the normal skin, however, they were confined almost always to the basal layer (where confusion with other "clear cells" is possible) while in the senile keratoses they occured here and scattered through the spinous cell layer as well. The dopa reaction for melanoblasts was not applied by us.

Microincineration preparations were made of all of the specimens. Scott (23) says that in normal epidermis there is a concentration of mineral ash in the distalmost layers of the epidermis and that the nuclei in the stratum germinativum stand out clearly although they do not have as much salt as in many other cell types. MacCardle (17, fig. 3 A and B) presents illustrations of skin of adult persons (40 and 50 years old respectively) in which all of the epidermal layers contain a heavy deposit of mineral.

The epidermis adjoining the keratotic lesions in our specimens contained a rather large amount of mineral matter, especially in the basal layer. Clear cells, however, were almost completely lacking in cytoplasmic ash. The spinous cells contained much ash, although less than the basal cells and ash was again abundant in the superficial layers, particularly in the stratum corneum.

The distribution of mineral ash in the keratoses was subject to considerable variation. This variation, however, seemed to correlate rather well with the histologic differences in different regions of any particular keratosis.

In the hyperplastic area, the amount of mineral ash in the spinous layer was generally very small (see fig. 17). In the basal layer, however, especially in the areas of down growth, the ash was quite abundant. The sparse quantities of ash in the spinous cell layer were definitely confined to certain portions of the cell, namely, the nucleolus, and a narrow zone of cytoplasm just outside of the

nucleus. In the basal cell layer the ash was mainly intranuclear.

In areas where the epidermis was relatively thin (figs. 15 and 16), or where it was actually atrophic, it contained greater amounts of ash than in the hyperplastic areas. Where parakeratosis was present, the ash content of the retained nuclei in the stratum corneum was considerable (fig. 16).

The ash of which we are speaking here was primarily the white ash of calcium and/or magnesium. It is safe to assume that it is mostly calcium. Scattered granules of red ash were seen in the dermis, but it was hard to relate their presence to any cellular structures.

In the masses of lymphoid cells in the dermis underlying the keratosis, the microincineration pictures revealed one feature of some interest. Between some of the heavily mineralized nuclei of these regions, delicate threads can be seen extending, forming a definite reticulum. Our material was not well fixed for reticular connective tissue stains, but we plan to use such stains in the future. It seems likely from the microincineration picture that actual, organized lymphoreticular tissue, rather than mere masses of wandering cells, exists in the dermis underlying some senile keratotic lesions.

Elastic tissue preparations (orcein) revealed definite changes in this tissue of the dermis (fig. 11). In the normal skin a branching network of well-defined, deeply staining fibers was seen. Under most of the keratosis the fibers appeared to be swollen, clumped, and lightly stained. It is interesting to note the sharp separation of the areas of lymphoid cells from the elastic tissue. In figure 11 the lymphoid cells are entirely between the elastic tissue and the epidermis, and this generally is true.

The cytochemical test for the ribonucleic acid of the epidermal layers brings to light no very marked deviation from the normal. There is apparently no such marked increase of ribonucleic acid in the immediately extranuclear cytoplasm as was referred to by Biesele (2) in epidermal carcinogenesis. All we can say is that in the basal cells easily detectable amounts of cytoplasmic ribonucleic acid occur. This is less in the lower layers of spinous cells and still less in amounts in the more superficial layers. In general, the distribution of ribonucleic acid in the normal epidermis is about the same. The spinous cell layer is in the normal state very narrow compared with that in the senile keratotic lesion. The nucleoli of all of the cells in the lesions contain abundant ribonucleic acid, even in the most superficial layers of the stratum germinativum. Clear cells stand out sharply in the basal layer, conspicuous by the lack of ribonucleic acid in their cytoplasm.

Whole mounts of epidermis from several keratoses have been prepared and further work by this method is planned. The preparations which have been made demonstrate the true papilliform shape of the epidermal down growths and the relative thinness of the epidermis in many places in the areas between such down growths (figs. 2 and 13).

Discussion

This study has been primarily a descriptive one. The multiplicity of these lesions and the difficulty of knowing the exact time of origin or stage of development of an individual lesion makes a discussion of the sequence of epidermal alterations a difficult task. The present survey, however, brings together observations on a number of lesions from different persons and attempts a more detailed investigation of cellular details than has been accomplished previously.

The combination of hypertrophic and atrophic change has seemed important to us. That a lesion which is producing an excess of keratin should ever present an atrophic epidermis is a rather surprising fact, yet in some of our sections where the lymphoid cells of the dermis were separated from the stratum corneum by only a few layers of flattened epidermal cells, the corneum itself was many times its normal thickness.

Scheideler (22) in describing hyperkeratosis in the region of the lymphatic ring of Waldeyer

speaks of areas where the epithelium is strongly atrophied, consisting of only 4 or 5 layers of cells, and with no well defined stratum Malpighi.

Hellman (12) in a case of tonsillar hyperkeratosis, describes the presence of a very thin epidermis, only a few cell layers in thickness, in the crypts, with a many layered epithelium elsewhere and with a thick cornified layer overlying all of the epidermis. He thinks that normally the leucocytes in the tonsillar epithelium exercise a dissolving action on the cornified layers and that in hyperkeratosis the normal reticularization of tonsillar epithelium is lacking.

We mention these two studies on hyperkeratosis in the pharynx because of the areas of atrophic epithelium described. The very large number of lymphoid cells often encountered in the dermis beneath the keratotic epidermal lesions might signify, if Hellman's concept is correct, a process tending to counteract a tendency to hyperkeratosis.

The areas of parakeratosis in our specimens have occurred in locations where the general contour of the epidermal layer had not been modified. Hagedoorn (11), in his description of a senile keratosis from the eyelid of a 56 year old man, found foci of parakeratosis only on papillae which had been thrust up above the general level of the epidermis. His description agrees with our finding that in such regions, where nuclei are retained in the cornified layer, a stratum granulosum usually is lacking.

The absence of pigment in the keratosis has been noted by Montgomery (18), Hagedoorn (11), and others and this absence, together with other features, serves to distinguish senile keratosis from verruca senilis.

Ruiter (21), who described a case of senile keratosis in a 24 year old woman—said to have had the lesion since she was 5 years old—also noted areas of parakeratosis accompanied by absence of a stratum granulosum, although a strongly developed granulosum was evident in other regions.

An explanation of some of the peculiar appearances of internal nuclear division (without mitosis) leading to two daughter nuclei in close apposition may be found in a recent paper by Lewis (16) concerning the mechanics of amitosis. He observed in tissue cultures some daughter nuclei in which loss of adhesion of the two nuclei was not complete. He considers this adhesion together of daughter nuclei to be occasioned by the same forces which hold together the individual chromosomal vesicles in the resting nucleus. Of these daughter nuclei adhering together (as in our fig. 6) he says (p. 438): "Such a condition can be explained by loss or partial loss of adhesion between vesicles better than by a constriction process."

We have not discovered any other reports of observations made on senile keratoses employing the technique of microincineration. Neoplastic tissues have been examined, however, in a general way by Scott and Horning (24). They found a definite increase in the amount of mineral ash present in various invading new growths as compared to corresponding normal tissue. They state that the increase within the cells corresponds well with the hyperchromatization of the nuclei, but that minerals in the cytoplasm also are increased.

Our observations, particularly on the more hyperplastic lesions, indicate a decrease in mineral content. This corresponds to some extent to the greater width of the spinous cell layer, but even individual cells are clearly poorer in ash than in the normal epidermis.

A decrease in calcium (calcium: nucleoprotein phosphorous) in the change from normal epidermis to precancerous hyperplasia and a further decrease in the change from precancerous hyperplasia to cancer was found by Suntzeff and Carruthers (27) by chemical rather than cytochemical methods. Chemical studies on senile keratosis are planned by us for the near future. A comparison of the results with data secured by microincineration will be of interest.

The question of differentiation of a senile keratosis from a carcinoma *in situ* is of course an important practical one. The presence of epithelial penetrations or down growths, as

Broders (3) points out, cannot be considered as a criterion of malignancy. The truest criteria for malignancy, he believes, should be sought for on a cellular basis. For the diagnosis of carcinoma *in situ*, based on cellular characteristics, he gives the following: "The nuclei, as compared with those of normal cells, have an increased avidity for the basophilic dyes, are usually increased in size, both actually, and in relation to the cytoplasm, are frequently irregular, are not infrequently in a state of atypical or pathologic mitosis and are occasionally observed in groups in the form of tumor giant cells."

Though the cellular characteristics of senile keratoses differ significantly from those of the normal epidermis, these lesions lack a number of the features mentioned by Broders as diagnostic of carcinoma *in situ*. Moreover they seem also to lack the very abnormal looking mitoses found in abundance by Blesele and Cowdry (2) in the epidermis of mice treated with methylcholanthrene long before the malignant transformation became manifest.

Finally, we would again stress the diversity of conditions observed in these human senile keratotic lesions. The deficiency in mineral residue in the spinous layer and the foci of atrophy suggest that in some parts of the lesions the cells are living under rather adverse conditions. These lesions are senile phenomena and in the epidermis of senile mice the calcium content is increased, not decreased. Moreover the human epidermis, near the lesions, is well supplied with mineral matter as far as we can tell microscopically.

The increase in number of cells (hyperplasia), on which the hypertrophy of certain regions of epidermis within the lesions depends, may obviously be due to decrease in cellular mortality as well as to increase in birth rate by mitosis. We have not made accurate determinations of mitotic frequency but the frequency within the lesions is not conspicuously different from that in neighboring epidermis, whereas, Cooper and Reller (4) found that in mouse epidermis 23 days after starting applications of methylcholanthrene the count increased from about 20 per 15,000 nuclei to approximately 150 per 15,000 nuclei. The 23 day period is far in advance of detectable malignancy.

Hyperplasia by increase in rate of production of new cells is, we believe, not a general feature of these lesions. The difficulty is that, having in mind the large cellular population of senile keratotic lesions, it is next to impossible to justify blanket statements concerning all of them. According to authorities the malignant transformation occurs in only a few of a great many cells. In this study and in others we hope to make, it is essential to relate the properties of the lesions determined cytochemically with a most accurate investigation of their appearance and characteristics *in situ* before excision.

Summary

In senile keratotic lesions hypertrophy of the epidermis, with many papilliform down growths, is often accompanied by areas of epidermal atrophy. Such areas of atrophy are particularly pronounced in 2 of our specimens.

Parakeratosis is frequently evident in the less hypertrophic and in the atrophic areas. In parakeratotic regions the stratum corneum retains its nuclei and a stratum granulosum generally is lacking.

The cellular features of senile keratosis include discrepancies in cell size, perinuclear vacuolization, hypertrophy of the nucleolus, tendency to internal division of the nucleus with vesicle formation, and amitotic nuclear division. Mitoses are not very common and pathologic mitoses have not been seen.

The distribution of mineral ash varies in accordance with the histologic features. In general, it is less abundant than in normal epidermis. No marked changes in amount of ribonucleic acid have been noted.

Frequently lymphocytes accumulate in the underlying dermis where there is also degeneration of elastic tissue.

The specimens of senile keratosis described in this paper were obtained from the Barnard Free Skin

DESCRIPTION OF PLATES

Fields shown in figs. 1 to 10 are from 5 sections stained with hematoxylin and eosin.

PLATE 1

Magnification of figures is X170.

FIG. 1. Normal skin from the neck of a 72 year old man immediately adjoining a senile keratosis.

FIG. 2. The keratosis from the same individual. Hyperplastic epithelium with many down growths. A dense mass of lymphoid cells in the dermis.

FIG. 3. An atrophic area of a senile keratosis from the cheek of a 79 year old man. A stratum granulosum is lacking and the stratum corneum is nucleated.

PLATE 2

Magnification of figures is X 1600.

FIG. 4. Two apparently adherent nuclei in a smaller cell. A perinuclear vacuole includes the pair.

FIG. 5. An internally divided nucleus, a large nucleolus in each portion. Keratosis from cheek of a 73 year old woman.

FIG. 6. Two adherent nuclei probably resulting from internal separation. Same subject as fig. 1.

FIG. 7. Two nuclei further separated. Cells with nuclei completely separate from each other are seldom seen. Same subject as fig. 4.

PLATE 3

Magnification of figures is X 1600.

FIG. 8. Spinous cell layer showing two common features of senile keratosis—discrepancy of cell size at the same level in the epidermis and the presence of perinuclear vacuoles.

FIG. 9. Spinous cell layer, showing a strong development of epithelial fibrillae. Keratosis from side of nose of a 40 year old man.

PLATE 4

FIG. 10. Small portion of a down growth in a keratosis from the cheek of a 73 year old woman. A metaphase is seen near the center of the field. In the lower left corner two lymphocytes in the epidermis. The down growths generally have a definite layer of columnar basal cells. X1600.

FIG. 11. Elastic tissue change in the dermis (on left of picture). The fibers are swollen, clumped, and lightly stained. Note the rather sharp limitation of elastic tissue against the lymphoid tissue. Lymphoid tissue and epidermis unstained. Orcein X400.

PLATE 5

Figs. 12 to 14 and 15 to 17 are from 5 sections, subjected to microincineration.

FIG. 12. Normal skin adjoining a keratosis (same subject as in fig. 1). Mineral ash fairly abundant in epidermis. X170.

FIG. 13. Hyperplastic epidermis of the keratosis. Little ash in spinous cell layer but considerable in basal cell layer, particularly of down growths. X170.

FIG. 14. Detail of lymphoid mass in dermis. The reticular structure suggests organized lymphoid tissue rather than wandering cells only. X400.

PLATE 6

FIG. 15. Parakeratotic region from a keratosis from side of nose of a 40 year old man. Mineral ash is fairly abundant throughout the epidermis and the nuclei of the stratum corneum show a dense deposit. X 400.

FIG. 16. Detail of same specimen. The perinuclear location of the ash in the spinous cell layer is well seen. X800.

FIG. 17. Region of hyperplastic epidermis from same subject as fig. 1. Very little ash present in the spinous cell layer. X800.

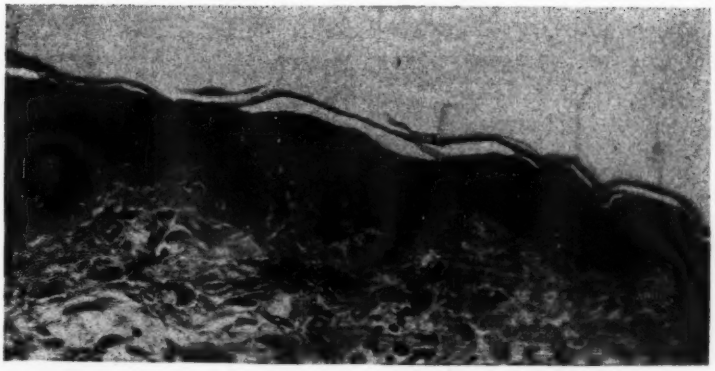

FIG. 1

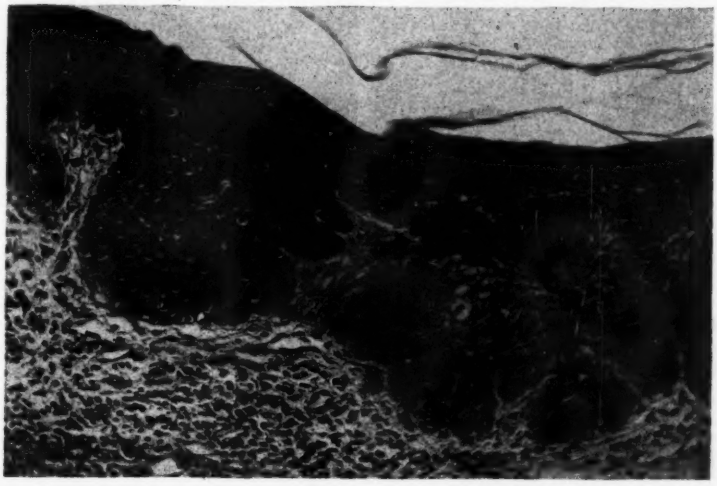

FIG. 2

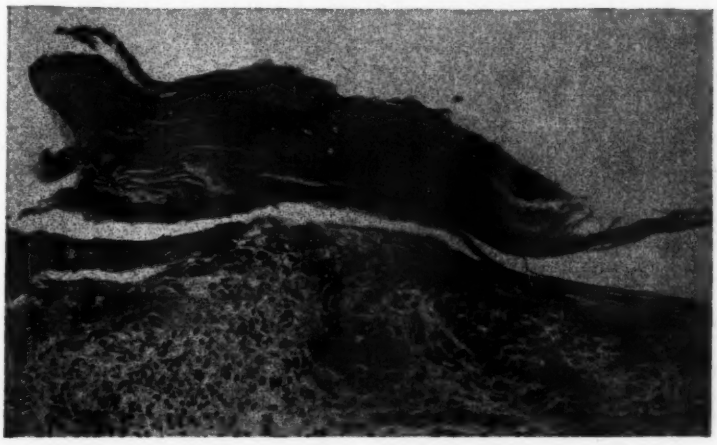

FIG. 3

PLATE 1

FIG. 4

FIG. 5

FIG. 6

FIG. 7

PLATE 2

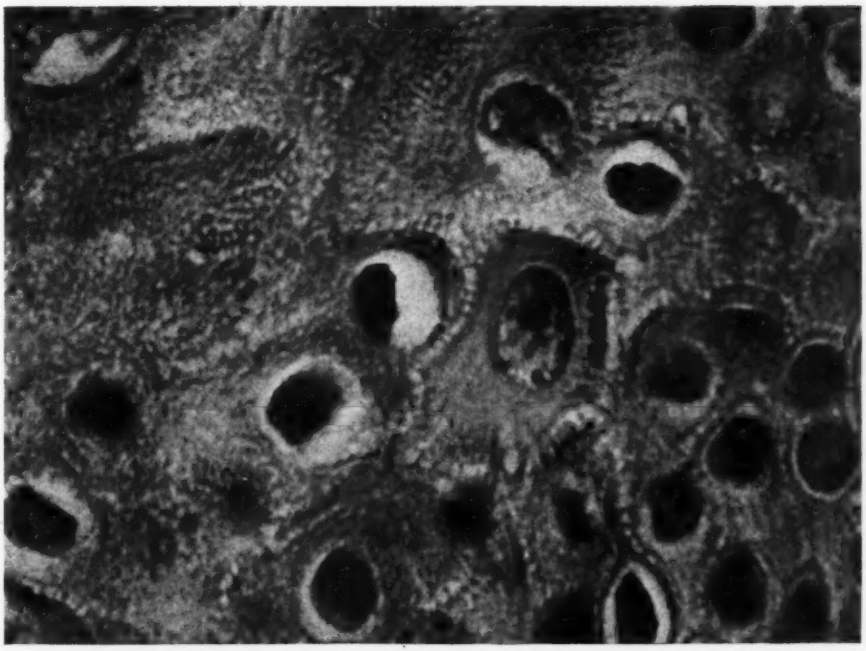

FIG. 8

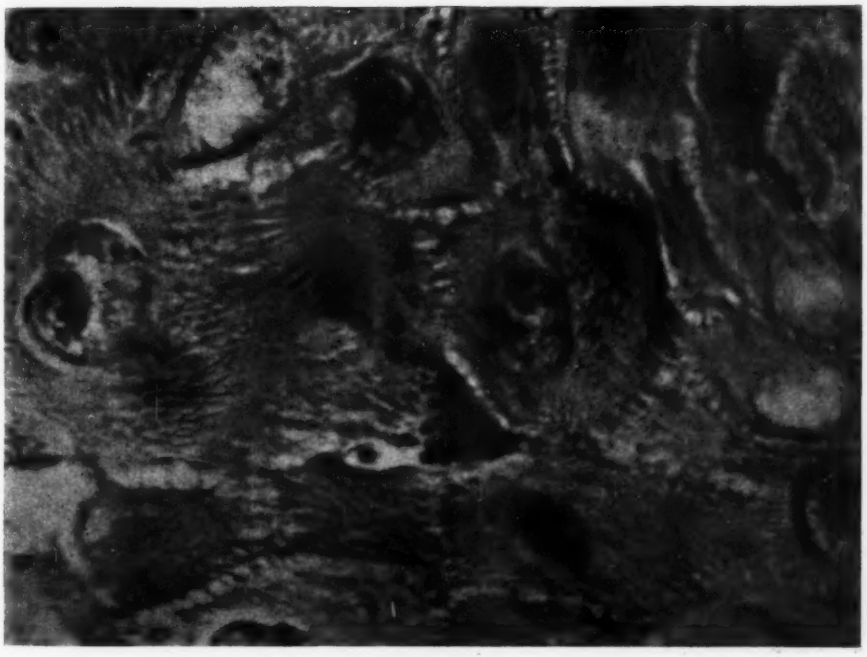

FIG. 9

PLATE 3

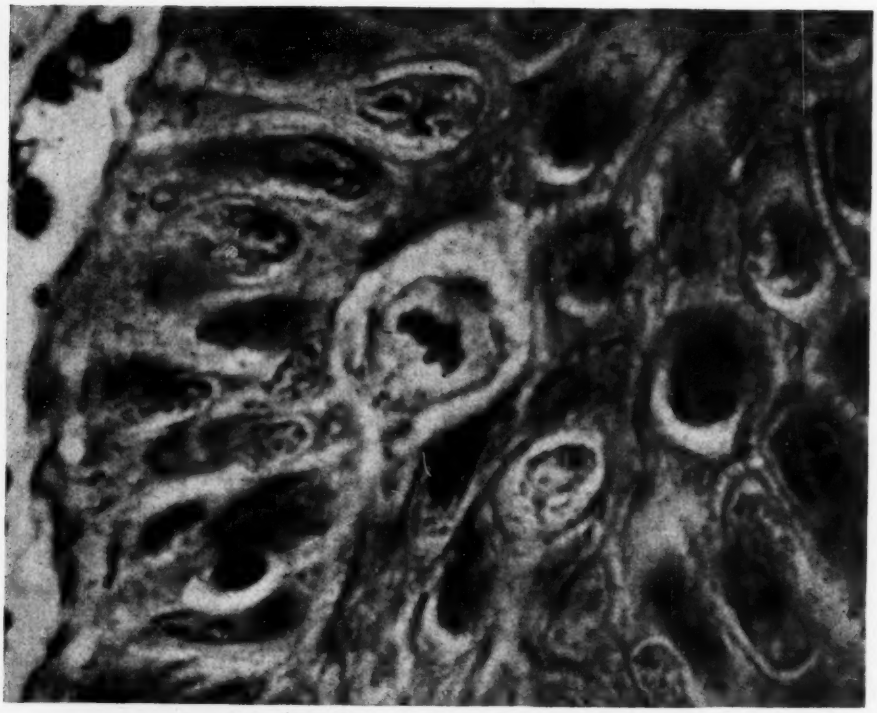

FIG. 10

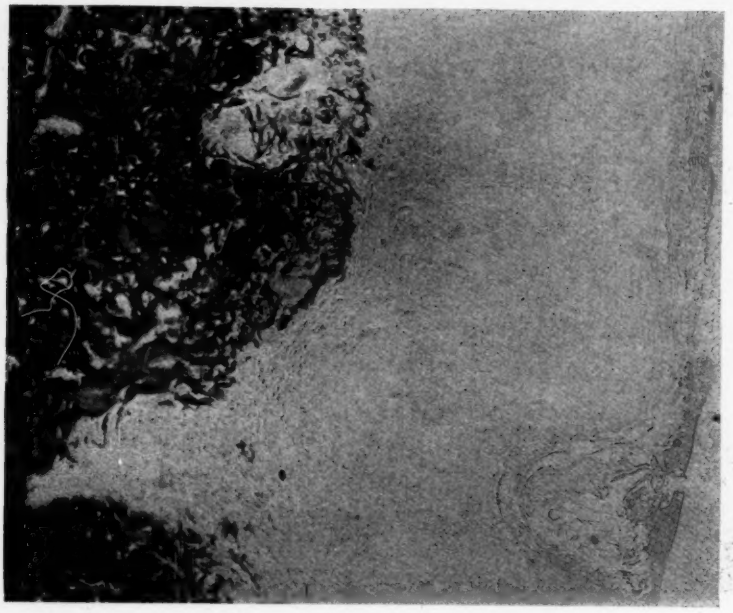

FIG. 11

PLATE 4

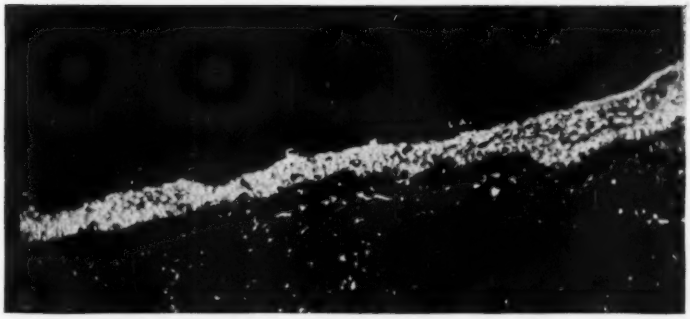

FIG. 12

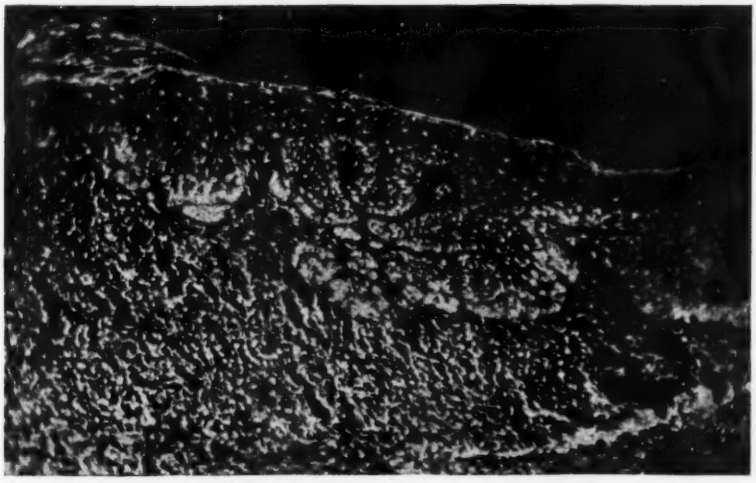

FIG. 13

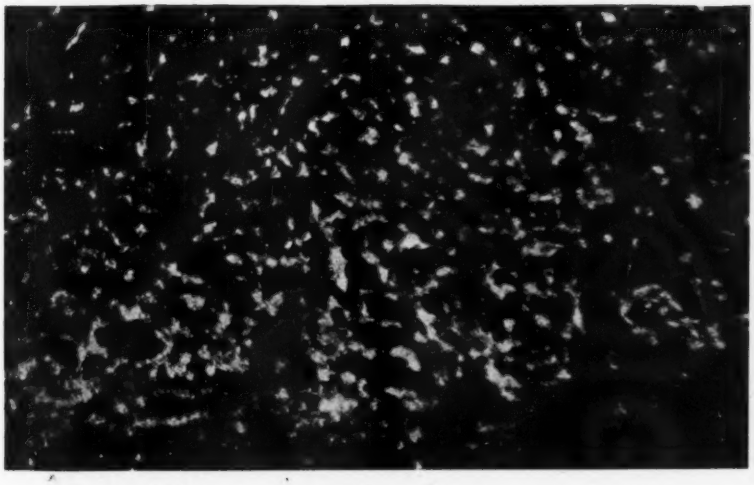

FIG. 14

PLATE 5

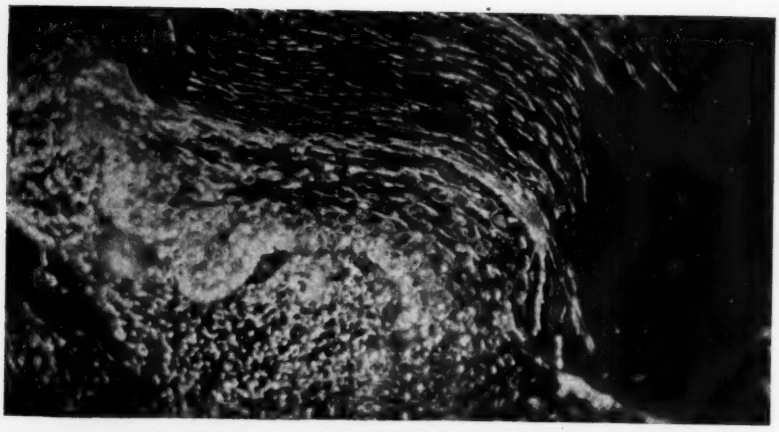

FIG. 15

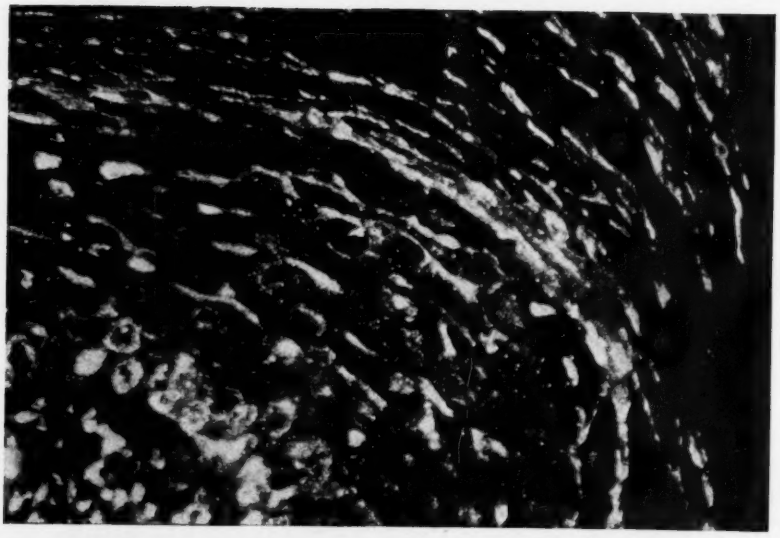

FIG. 16

FIG. 17

PLATE 6

and Cancer Hospital, St. Louis, through the cooperation of Dr. Richard S. Weiss, Chairman of the Department of Dermatology at Washington University, and Dr. Herbert Joseph, Resident in Dermatology at Barnard Hospital.

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Calcium and Elastin in Human Arteriosclerosis

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DOCTORS LANSING, ALEX, AND ROSENTHAL PROPOSE THAT IN HUMAN ARTERIOSCLEROSIS THE FORMATION OF INTIMAL PLAQUES IS CONDITIONED TO A LARGE EXTENT BY DEGENERATION AND CALCIFICATION OF ELASTIC FIBERS IN THE MEDIA OF THE ARTERY. IN SUPPORT OF THIS CONCEPT THEY ARE REVIEWING EARLIER DATA FROM THEIR LABORATORY AND ARE PRESENTING NEW PERTINENT EXPERIMENTAL OBSERVATIONS. THE SUBSTANCE OF THIS PAPER WAS DELIVERED AT THE SECOND ANNUAL SCIENTIFIC MEETING OF THE GERONTOLOGICAL SOCIETY HELD IN CHICAGO, NOVEMBER 5-6, 1949.

It is reasonably safe to say that much of the confusion in the literature concerning arteriosclerosis could be dispelled if there were some measure of agreement as to what is meant by the term arteriosclerosis. At the present time the dominant belief seems to be that atherosclerosis and arteriosclerosis are synonymous; in other words, that changes in the intima such as fibrosis and cholesterol deposition constitute the essential features of "hardening of arteries." Medial calcinosis, believed to be restricted to muscular arteries (Mönckeberg's sclerosis), is held to be a lesion independent of arteriosclerosis.

This latter view was clearly shown to be incorrect by Blumenthal, Lansing, and Wheeler (3) whose data on human aortas indicated that "calcification of the media precedes the formation of intimal plaques; that medial calcification occurs more frequently than do intimal plaques; that intimal plaques do not occur without calcification of the media or other medial change such as syphilitic aortitis, or marked connective tissue infiltration of the media; and that within a single aorta medial calcification is probably more intense in the immediate vicinity of an intimal plaque than elsewhere." Calcification, then, occurs in elastic as well as muscular arteries.

More recently, Lansing, Blumenthal, and Gray (7) reported their observations on the human coronary artery and concluded that in this vessel as in the aorta there is a progressive increase of calcium in the media with advancing age. Calcium is apparently deposited quite specifically in or on elastic tissue in the media, and medial calcification and elastic tissue changes are more pronounced under atheromatous plaques than elsewhere in the same vessel.

These observations were extended to include the hepatic, renal, and iliac arteries (Blumenthal, Lansing, and Alex, 2). As in the coronary artery, these vessels manifested progressive alteration of the medial elastic tissue and calcification thereof with advancing age.

It seems to us that we must revive the view entertained quite widely a few decades ago that arteriosclerosis is a problem of aging and that the changes of arteriosclerosis are a product of alteration of medial elastic tissue. A good review of this concept of arteriosclerosis is offered by Wells (12).

In an uncompromising vein Wells (12) wrote as follows: "It would seem that the changes of arteriosclerosis appear whenever the elastic elements of the media yield permanently . . . . . With advancing years the capacity to regenerate damaged elastic tissue is apparently reduced . . . . ."

Summarizing the pattern of arteriosclerosis in mammals and birds Fox (4) stated: "The relations of atheroma and elastica and of muscle and calcium seem definite in some places. The part played by elastic tissue in calcification has not been determined and the only feature that is clear is that the less definite the lamina protecting the media, the more definite is the atherosclerosis."

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Dr. Rosenthal is research associate in the Department of Anatomy, Washington University School of Medicine. He received his Ph.D. degree in 1941 from Yale. From 1941 to 1945 he served with the Army Air Force as an aviation physiologist. He was a research associate at Barnard Free Skin and Cancer Hospital, St. Louis, 1946-1948, before taking his present position. Biophysics and cancer are his chief research interests.

The disfavor into which this concept of arteriosclerosis has fallen is due almost entirely to the finding of Anitschkow (1) that atheromata may be experimentally produced by the administration of cholesterol.

At this point it seems pertinent to recall the opening remark of this paper. What is arteriosclerosis? Are the terms arteriosclerosis and atherosclerosis synonymous? We believe that they are not. For the purpose of this discussion, atherosclerosis will be defined as a process involving fatty and fibrotic degeneration of the intima of vessels while arteriosclerosis will be defined as an age dependent process of fatty and fibrotic degeneration of the intima accompanied by and generally preceded by calcification of medial elastic tissue.

In reaffirming the idea that arteriosclerosis is a problem of aging we accept the possibility that faulty cholesterol metabolism may be involved. It is entirely possible that the medial calcinosis we have described in both elastic and muscular arteries may be produced by altered lipid metabolism. There is no evidence at the present time for or against this view. In this paper we wish to recapitulate some existing data on arteriosclerosis and to present new data on the relation between elastic tissue changes and medial calcification.

Age Incidence of Intimal Sclerosis and Medial Calcification:

As previously stated, the study of Blumenthal, Lansing, and Wheeler (3) concluded that calcification of the media of the aorta precedes the formation of intimal plaques. This conclusion was based upon histologic and microchemical analysis of 540 human aortas. Medial calcification was present in 4 per cent of the aortas of persons less than 20 years of age, in 23 per cent of persons 20 to 30 years old, in 58 per cent of persons 30 to 40 years old, and in essentially 100 per cent of persons over 50 years of age.

In the same series of specimens, intimal sclerosis was found in only 4 per cent of individuals 20 to 30 years old, in 27 per cent of individuals 30 to 40 years old, and intimal sclerosis finally reached a maximum incidence slightly over 80 per cent in the ninth decade of life. The incidence of intimal sclerosis of the human aorta lags behind medial calcification of that vessel by approximately one decade.

Cholesterol Deposition, Intimal Plaques, and Medial Calcification:

Understanding of the sequence of events associated with the production of human arteriosclerosis is essential to a rational approach to the problem; unfortunately, in the human this is not subject to direct and continuous observation in the individual. One must de-

pend upon the method of seriation. Karsner (6) proposes the sequence of changes in arteriosclerosis as fibrosis, hyalinization, atheroma, and finally calcification. The data we have offered clearly indicate that calcification precedes the formation of intimal plaques. The question we are primarily concerned with is whether medial calcification predisposes the artery to atheromata.

A clue to the possible relation between elastic tissue and calcific changes in the media and atheromata may be obtained from histologic examination of arteries. In a survey of age changes in the human left coronary artery based largely on elastic tissue staining with resorcin fuchsin and darkfield examination of microincinerated sections Lansing, Blumenthal, and Gray (7) noted that elastic tissue fragmentation and calcification thereof was much more intense immediately under an atheromatous plaque than in areas adjacent to the plaque.

Figure 2 illustrates a large plaque in the left coronary artery of a 79 year old subject. A dense band of elastic tissue of abnormal appearance courses along the base of the plaque in the region of junction of the intima and media. This situation contrasts quite sharply with an area less than 1 mm. away from the edge of the plaque (fig. 4). The pattern of accumulation of fragmented elastic fibers is much less intense in this relatively normal field than under the plaque. An equally sharp contrast is obtained by examination of the microincinerated sections which are illustrated in figures 3 and 5. The latter shows that there is but little mineralization of the relatively normal appearing elastic tissue of the internal elastic lamella while the specimen illustrating the plaque reveals a heavy deposit of the white ash of calcium in and about the aberrant elastic tissue.

Insofar as we have been able to determine this phenomenon holds true quite generally. Calcification of fragmented elastic tissue under an intimal plaque is much more pronounced than in adjacent areas of the artery free of plaques. Further, elastic tissue calcification occurs without intimal plaque formation but the converse does not seem to occur. This may mean that elastic tissue breakdown and its consequent calcification predispose the vessel to intimal plaque formation but are not solely operative. Perhaps disruption of the vasa vasorum as a consequence of medial changes is the second variable.

In this respect it is worth while to consider the manner of deposition of cholesterol in intimal plaques. Figure 1 represents a large plaque in a senile left coronary artery stained with hematoxylin-eosin. It is readily apparent that the nidus of cholesterol crystals lies near the base of the plaque and is covered by a layer of fibrous connective tissue at least 1 mm. thick. It is difficult to conceive of the cholesterol penetrating the endothelium and coursing through the thick mass of fibrous tissue oriented in an axis perpendicular to the hypothetic path of the cholesterol droplet to finally lodge near the media.

Leary (8), however, believes that the cholesterol droplet does pierce the endothelium to lodge in the intima and that fibrosis develops in response to cholesterol infiltration. More data are needed to resolve this problem. Histologically, one sees in the small, formative plaque little else but fibrous connective tissue; it is only in the larger and presumably older intimal plaques that cholesterol deposits may be observed as in figure 1.

Observations on the Human Pulmonary Artery:

The pulmonary artery is of particular interest in a study such as this since it is uncommon to find atheromatous changes in it. If the breakdown and calcification of elastic tissue in an artery is a precursor to intimal plaque formation then a vessel such as the senile pulmonary artery should not exhibit the elastic tissue changes. This problem is under study by Blumenthal, and the conclusions will be reported in detail elsewhere. On a preliminary basis, the findings are sufficiently clear-cut to warrant introduction here.

Figure 6 illustrates a section of the pulmonary artery of a 21 year old colored female

stained by the method of Verhoeff for elastic tissue. The elastic fibers are thick, compact, and exhibit little or no fraying. The dark field photomicrograph (fig. 7) of the microincinerated section reveals the characteristic low mineral content of a young vessel. For comparison with this young specimen figures 8 and 9 illustrate sections of the pulmonary artery of a 67 year old female stained for elastic tissue and microincinerated to reveal mineral content and distribution. In the resorcin-fuchsin preparation the elastic fibers are surprisingly intact with little or no fragmentation fraying. The darkfield photomicrograph of the microincinerated specimen indicates little or no mineral change in elastic fibers of the media.

This lack of elastic tissue breakdown and calcification of the senile pulmonary seems to support our view that this phenomenon is generally a precursor to atheromatosis. Through the cooperation of Dr. John J. Connor we have been able to procure the pulmonary artery of a 69 year old white male which is markedly atheromatous. In this vessel the elastic fibers are thin, fragmented, and frayed and there are small clusters of granular material scattered throughout the media which stain like elastic fibers (fig. 10).

The microincinerated section reveals a dense band of mineral ash, largely calcium, which courses through the media and corresponds largely to the distribution of the elastic fibers (fig. 11). The pattern of elastic tissue breakdown and of calcification in this specimen is strikingly similar to that which we have described in senile aortas. The indications, once again, are that elastic tissue degeneration and calcification are intimately associated with atheromatosis and that in the absence of the former, the latter generally does not occur.

Analytic Data on Elastin and Calcium Changes with Age:

Quantitative analytic methods were employed to reinforce the data acquired by microscopic procedures and to gain information on the nature of the age changes in elastin which make the deposition of calcium possible.

Elastin was prepared from human aortas by a modification of Lowry's method (9). The intima and adventitia of the fresh aorta were stripped free and discarded leaving the media for further analysis. The media was refluxed in acetone and ether from which defatted media the elastin was extracted by treatment with 0.1 N NaOH for forty-five minutes at 98 C. The elastin was dried at 105 C. and weighed. The calcium content of the dried elastin was determined by the method of Salomon, Gabrio, and Smith (11).

TABLE 1. COMPARISON OF ELASTIN AND CALCIUM CHANGES WITH AGE IN HUMAN AORTAS.

Decade	Number of Analyses	Percentage of Elastin*	Percentage of Calcium†
0-10	5	48.5	0.7
11-20	5	48.2	0.4
21-30	15	43.3	1.2
31-40	7	41.4	1.9
41-50	11	44.1	4.7
51-60	17	41.4	6.6
61-70	30	43.8	5.1
71-80	14	43.8	6.9
81-103	6	41.1	5.5

The analyses were performed on defatted, dessicated medias (stripped free of both intima and adventitia).

* Average per cent elastin in defatted, desiccated media.

† Average per cent calcium in dry elastin.

The results obtained by these procedures on aortas ranging in age from stillborn to 103 years are summarized in table 1. The average elastin content of the media during the first two decades of life is slightly over 48 per cent while the average elastin content in the third decade and thereafter drops to values ranging between 41.1 and 44.1 per cent. Because of the limited number of specimens available for analysis in the first two decades it is difficult to decide whether or not this apparent drop

in medial elastin content is significant. Certainly there is no significant gain or loss of elastin after the third decade of life.

The average percentage of calcium in dry elastin is at a very low level during the first two decades (0.7 and 0.4). In the third decade, there is a sharp rise in the calcium content of elastin, which continues to increase through the fifth decade of life, after which the content of calcium seems to reach a maximum of about 6 per cent.

What age change occurs in elastin that results in increased calcium binding? A clue to a possible mechanism was derived from amino acid analyses by two dimensional paper chromatography under the supervision of E. Roberts. His procedures for paper chromatography are described elsewhere (10). Chromatograms of the amino acids of elastin from young aortas show a small amount of the dicarboxylic amino acids. Glutamic acid is present in low concentrations and aspartic is essentially absent. On the other hand, chromatograms of old elastin show roughly the same concentration of glutamic acid (per unit of nitrogen) but markedly denser spots for aspartic acid.

This observation was quantitated for us by G. B. Ramasarma using the method of microbiologic assay described by Henderson, Brickson, and Snell (5). Analysis of 6 young and 6 old samples of elastin gave the following averages:

MICROGRAMS PER MILLIGRAM DRY WEIGHT

	Glutamic Acid	Aspartic Acid
Young	23.8	6.12
Old	28.7	12.21

An increase in the acidic groups of the protein or proteins of elastin would certainly result in increased base binding capacity. It is a temptation to speculate that the increased acidity of elastin resulting from a doubling of the aspartic acid content thereof is responsible for the increased affinity of elastin for calcium. Until further data are available we can only consider this as an interesting possibility.

SUMMARY

New emphasis is placed upon the concept that arteriosclerosis is a problem of aging and that the changes of arteriosclerosis are a product of alteration of medial elastic tissue. Observations are discussed which lead to the following conclusions:

1. Medial calcification precedes the formation of intimal plaques.
2. Elastic tissue changes involving calcification of the elastic tissue are more severe under a plaque than in areas adjacent to the plaque.
3. Senile pulmonary arteries free of atheroma are also free of the elastic tissue and calcific changes.

Quantitative analytic data are presented which indicate that after the age of 20 years there is no change in the elastin content of the media of the aorta. There is a sharp increase in the calcium content of elastin at this age which increases steadily to reach a maximum at approximately 50 years of age.

Amino acid analyses of young and old elastin reveal a significant increase of aspartic acid with age. It is suggested that this shift in the composition of elastin with age may account for the increased calcium content.

This investigation was supported by a grant from the American Foundation for High Blood Pressure.

We are particularly indebted to Dr. John J. Connor, Chief Pathologist, Coronor's Office, City of St. Louis, for his generous cooperation in the procurement of material for these studies. Without his aid this work could not have been done.

We wish to thank Dr. E. Roberts, Department of Anatomy, and Dr. G. B. Ramasarma, Departments of Surgery and Bacteriology, Washington University School of Medicine, for their assistance with the chromatography and bio-assays.

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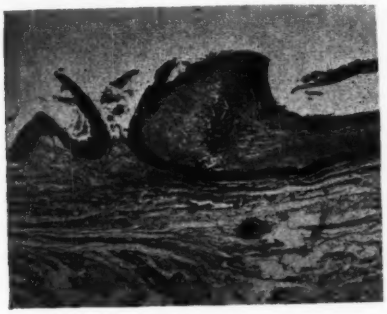

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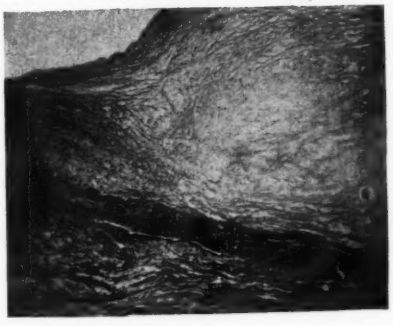

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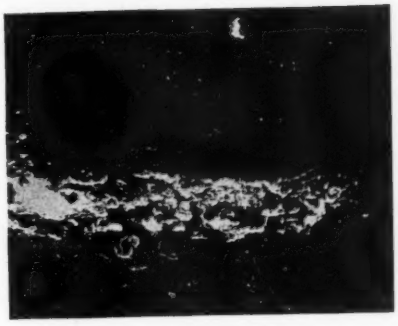

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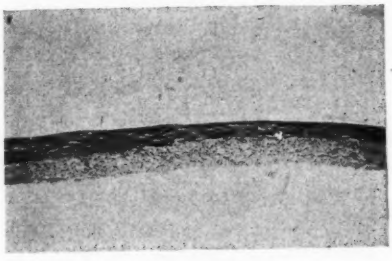

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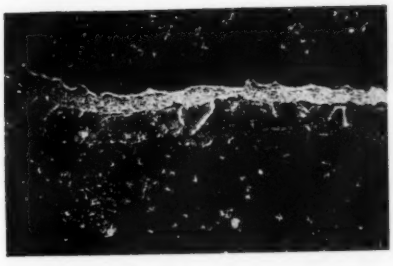

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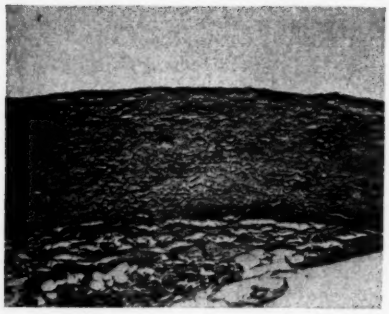
FIG. 1. Section through the coronary artery of a 79 year old male containing a large plaque with a cholesterol mass at the base of the plaque. Hematoxylin-eosin. 10 X.

FIG. 2. Same specimen as in Fig. 1 stained with resorcin fuchsin showing dense band of elastic tissue at base of plaque. 50 X.

FIG. 3. Same as Fig. 2 but microincinerated to reveal mineral distributions. Darkfield, 50 X.

FIG. 4. Resorcin fuchsin stained section of above artery from an area adjacent to the plaque. 50 X.

FIG. 5. Same as Fig. 4 by microincineration to show mineral pattern. Darkfield, 50 X.



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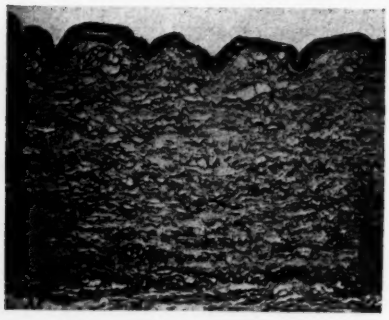

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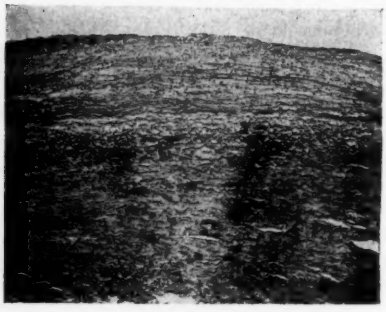

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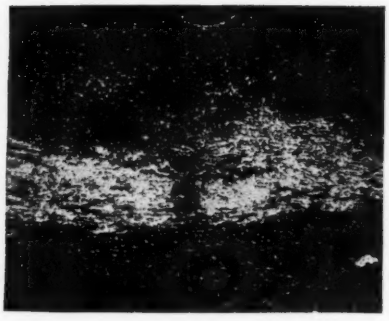

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FIG. 6. Pulmonary artery of a 21 year old colored female. Verhoeff's elastic stain, 50 X.

FIG. 7. Microincinerated section of specimen shown in Fig. 6. Darkfield, 50 X.

FIG. 8. Pulmonary artery of a 67 year old white female. Resorcin fuchsin, 50 X.

FIG. 9. Microincinerated section of specimen shown in Fig. 8. Darkfield, 50 X.

FIG. 10. Pulmonary artery of a 69 year old male with intimal plaques. Verhoeff's elastic stain, 50 X.

FIG. 11. Microincinerated section of specimen shown in Fig. 10. Darkfield, 50 X.

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Treatment of Senescence in Female Rats with Sex and Thyroid Hormones

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IN PREVIOUS EXPERIMENTS THE EFFECTS OF HORMONES ON OVARIECTOMIZED RATS WERE INVESTIGATED. IN THE PRESENT SERIES THE EFFECTS OF HORMONES ON INTACT SENESCENT RATS WERE FOUND TO BE SIMILIAR BUT IN SOME WAYS WEAKER THAN ON THE FORMER GROUPS.

IN previous papers (22, 24, 36, 37, 38) the effects of sex and thyroid hormones were investigated on some processes of aging, accelerated by ovariectomy, in adult female rats. The plurihormonal treatment used stopped aging involution of some organs and brought the relative weights of these organs towards or up to the level observed at a younger age. Simultaneously, however, with this stimulating and apparently favourable effect, in some of these organs certain pathologic or depressing effects were observed.

In the present paper treatment with the same hormones has been applied to senescent normal intact female rats.

There are, as far as we know, only three papers on the effects of hormones on the senescence of female rats.

Steinach (56, p. 63) described very briefly the results of implantation of ovarian grafts, taken from young rats, into senile rats. About four weeks after the operation oestrus appeared, the fur started to grow thicker, and the rats gained in weight.

Steinach, Heinlein, and Wiesner (57) injected normal rats, about 19 to 22 months old, with an ovarian extract. After only four injections, oestrus cycles, which had ceased some time prior to the injections, appeared again and continued to be normal during the period of observation without any repetition of the injections, indicating that the ovary was regenerated. The animals gained about 30 Gm. in weight; their appetite increased; their fur, which had been poor, dirty, and bald in patches, became normal; their clumsy and slow movements and apathetic senile behaviour changed into those usual for young or adult rats.

Before the injections biopsy of one horn of the uterus disclosed that it was atrophic with a fibrous mucosa. After the injections the structure of the uterus acquired all the features of that of an adult normal rat.

Zondek (64) injected oestrone into senile rats and also observed that after only one injection a normal lasting oestrus appeared.

There are also a number of papers in which the action of hormones on adult normal female rats has been studied. Some of these investigations which help the interpretation of the present experiments will be referred to.

Thus, Korenchevsky, Dennison, and Hall (27, 28) found that after three weeks of daily injections with 0.5 to 1.5 mg. of testosterone propionate (weekly dose of 3.5 to 10.5 mg.) the uterus, vagina, and preputial glands were greatly hypertrophied, the kidneys and, with a larger dose, the ovaries, increased in weight, involution of the thymus was much accelerated, and fat deposition decreased. There were no definite changes in the weight of the other organs investigated nor in the body weight. The effect of pure testosterone was weaker.

Histologic investigation (28, 29) showed great hypertrophy of all layers of the uterus and vagina, with a pregnancy-like lacy mucosa of a normal or cystic structure in the uterus, and mucified, also pregnancy-like, vaginal epithelium.

In the experiments of a longer duration (53 to 146 days) androgens and oestrogens were

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In 1945 Dr. Korenchevsky was appointed head of the Gerontological Research Unit at Oxford, establishment of which was made possible by a grant from Lord Nuffield. The subjects of research in which Dr. Korenchevsky is most interested include gerontology, endocrinology and the study of vitamins.

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administered separately or together (32). The doses of androgens varied from 2.25 to 7.5 mg. per week; the doses of oestradiol benzoate-butyrate were 0.09 mg. The uterus was either unchanged or atrophied with smaller doses of testosterone propionate. This was because the depressing effect on the hypophysis of small doses could not be counterbalanced by their direct stimulating action on the uterus itself. Large doses, on the contrary, produced gigantic uteri as in the experiments of three weeks' duration. The vagina was hypertrophied with both small and large doses, and the vaginal epithelium was mucified to different degrees.

The first stage of the effect of male hormones on the ovaries was a follicle-stimulating action; the second stage, a luteinising effect; in the third stage this gonadotropic action of androgens was replaced by a toxic action, producing atrophy of the ovaries (32, figs. 12, 13, 18-22).

Oestrogens, depending on the dose, produced luteinising or atrophying effects on the ovaries, i. e., the second and third stages (32, figs. 14, 15, 23). The uterus, although hypertrophied, showed fibrous structure of the mucosa, which was oedematous in places, had cystic enlargement of some glands, and irregular development of the myometrium. The vagina was hypertrophied, with more or less mucified epithelium.

Combined injections of androgens and oestrogens produced similar changes in the sex organs, but in the ovaries the formation of cysts, sometimes large ones, was a common feature (32, figs. 16, 17, 24-27).

In other previous papers (33, 35) experiments were described on the effects of comparatively large but nontoxic doses of thyroid hormone on the weights of organs and histologic changes in the thyroid, liver, and kidneys in normal female rats.

It is important to keep the rats on a diet rich in vitamins (as is done in all our experiments) when comparatively large doses of thyroid hormone are given if toxic effects of these doses are to be prevented (11, 35). The effects produced by nontoxic doses of thyroid hormone may be summarised briefly as follows: hypertrophy of the adrenals, liver, kidneys, spleen, heart, and ovaries, depression of the thyroid gland, and reduction of body fat.

In the experiments by Selye on intact rats (51, 52) progesterone given in enormous doses (10 mg. daily for 20 days) produced hypoplasia of the adrenals, progestational changes in the uterus and vagina, and enlargement of the preputial glands and mammary glands. In another experiment of twenty-one days' duration (53) on 96 intact young female rats Selye investigated the effects of various hormones on the actual weight of different organs in the

following daily doses: oestradiol 0.3 mg., progesterone and pure testosterone 2 mg. One control group was injected with pure oil and another with 6 mg. of cholesterol in oily solution. In spite of very large doses of the hormones the changes obtained were small. No statistical analysis was used.

Selye concluded that gain in body weight was increased by progesterone and was depressed by oestradiol. Progesterone, testosterone, and oestradiol decreased the weight of the ovaries. Oestradiol enlarged but testosterone and progesterone decreased the weight of the adrenals. The kidneys and preputial glands were enlarged by testosterone and decreased by oestradiol. The uterus was enlarged by testosterone and oestradiol but involution of the thymus was accelerated by both these hormones. No definite effect of progesterone, oestradiol, or testosterone, given alone or in combination, was observed on the thyroid, liver, spleen, or heart.

In the following paper (54) Selye and Beland performed similar experiments but of longer duration (three months). The complicated arrangement of this experiment makes difficult the comparison of changes obtained in the weights of organs in various groups, especially since the results were not examined statistically. The daily doses of oestradiol (0.05 to 0.2 mg.), testosterone and progesterone (0.5 to 2 mg.) were large, particularly if the length of the period of injections is taken into consideration.

The authors recorded the following changes: oestradiol enlarged the hypophysis with development of adenoma in some cases, produced enlargement of the adrenals, involution of the thymus with reversion to the epithelioid embryonic type, also sclerosis of the uterus and atrophy of the ovaries. Testosterone, and to a lesser degree progesterone, produced mild enlargement of the kidneys and progestational changes in the uterus. Involution of the thymus was caused by testosterone but not by progesterone. The authors concluded that no definite changes were present in the weight of the thyroid, pancreas, liver, spleen, or heart, although the weight of the three latter organs was considerably increased after treatment with certain hormones.

In the experiments of Ross and Korenchevsky (50), confirmed by Plagge (46, 47), interesting epithelioid adenoma-like structures were observed in the thymus after administration of oestrogens.

This summary of the literature referring to the effects of hormones on young, adult, or senile intact female rats supplements that reviewed in the previously cited papers (22, 32, 33, 35, 36, 37, 38), and provides data for comparison with, and in some cases confirmation of, the results obtained in the present experiments on senescent rats.

Methods

Two experiments were performed on a total of 121 female normal senescent rats aged about 27 months in experiment I and about 22 to 24 months in experiment II. The duration of the experiments was 60 and 86 days respectively.

The arrangement of the experiments into various groups and the amounts of hormones administered to each group are shown in tables 2 and 3. All animals were killed by bleeding.

In the present experiments a different strain of rats was used from that described in the previous papers. Therefore, for the comparison of relative weights of organs of senescent rats with those of young rats, in table 1 the data are given only from the animals belonging to the same strain. Thus, 14 young rats were killed at an average age of 53 days and they were compared with 25 senescent rats. The group of senescent animals consisted of 17 control rats of present experiments I and II pooled together with 8 senescent rats from another experiment performed on the same strain.

Androsterone and progesterone in both experiments and testosterone propionate in experiment I were injected subcutaneously as crystals suspended in a 5 per cent aqueous solution of gum acacia. In experiment II testosterone propionate was implanted in the form of 20 mg. pellets and was absorbed at an average

rate of about 1.07 mg. a week. Oestradiol 3-benzoate-17-n-butyrate was dissolved in sesame oil, and 0.2 cc. of the solution injected subcutaneously. The effects of this oestradiol compound, because of its very slow absorption, lasts at least three and a half months (probably longer) after the final injection (26).

Desiccated thyroid was administered by pipette in the form of a sweetened emulsion containing 5 per cent of gum acacia.

All organs were fixed in Bouin's fixative and weighed after fixation. The dissected retroperitoneal fat and the fat attached to the sex organs were weighed together and represent the abdominal fat listed in the tables.

For histologic investigation the organs were embedded in paraffin wax and stained with Ehrlich's haematoxylin and eosin, or, when required, with Mayer's mucicarmine or Masson's trichrome stain. Frozen sections were also cut and stained with sudan-black for fatty substances.

Measurements of liver cells and renal tubules were made by the method of paper replicas which has been described previously (22). Measurements of adrenocortical zones, projected and outlined on paper, were made by planimeter.

Measurement of the cardiac muscle fibres is very difficult because of considerable variation in their diameter. Paris tried various methods and found that of Aschoff (2) for the human heart also the best for the rat. This procedure consists of ascertaining the percentage of large muscular fibres to the total number of fibres in two ribbons across the wall of the left ventricle, thus giving two counts of approximately 300 fibres.

These two counts were found to be sufficient for statistical analysis of changes between the groups. Those fibres which measured 16μ or more in diameter and which were in a more or less constant minority in the control rats were designated large fibres. All the results expressed in figures were statistically analysed by Benjamin using Fisher's t-test for small samples; this is Benjamin's contribution to the present paper. When two P values are given (e. g., $P < 0.05$-0.001), it is meant to designate that the values were different in the different groups referred to, lying on a certain figure between the limits quoted.

General Appearance of the Rats; Changes in Body Weight and Fat Deposition

The main difference between experiments I and II was in the amount of the doses of androsterone and testosterone propionate: in experiment I a considerably smaller dose of androsterone and a considerably larger dose of testosterone were used as compared with those of experiment II. This should explain the weaker effect of the former and some toxic effects of the latter in experiment I.

As compared with the control rats, a definitely healthier appearance of the rats, as judged by the condition of their thick and glossy fur, the total, or comparative, absence of patches of thin fur (baldness), and the roundish lines of a well nourished body, was observed only in three groups: in the progesterone + oestradiol group (the best appearance), the oestradiol group, and the androsterone group.

The rats in experiment I injected with large doses of testosterone propionate looked definitely poorer than those in the control groups. They were thinner, with rough fur and patches of baldness, and gave the impression of animals depressed under the toxic action of this hormone. The rats to which desiccated thyroid was administered were thinner but had good fur and were healthy-looking animals. In the other groups the appearance of the rats was more or less similar to that of the controls.

In accordance with the external appearance of the senescent rats in both experiments, gain in bodyweight and fat deposition were especially good in the progesterone + oestradiol group, the androsterone group, and, to a lesser degree, in the oestradiol group.

The comparatively small doses of thyroid hormone used in our experiments produced a small and statistically not significant decrease in body weight and fat deposition. This de-

crease was more or less neutralised by androsterone in the groups simultaneously injected with the four hormones. This indicates that androsterone, a natural female androgen, in the combinations used seems to have a more beneficial effect than testosterone on senescent female rats.

The difference in amounts of body fat in young and senescent rats (table 1) as well as in different groups of the latter emphasizes once more the conclusion repeatedly made in our previous papers that for comparison of relative weights of organs these weights have to be calculated per unit of fat-free body weight.

In our experiments only a rough and approximate method of estimation of body fat was used, as has been previously described (34, 36). It is important to work out a more accurate one.

Ovaries

Features of Aging.—The aging hypoplasia of the ovaries is shown in table 1 ($P < 0.01$). Histologically about 70 per cent of the control senescent rats had an apparently normal structure of the ovaries. In about 30 per cent, however, the number and size of the follicles and corpora lutea in the ovaries decreased while the area of interstitial cells and stroma elements predominated. This can be observed when comparing figure 1 with figure 2, the latter being a photomicrograph of a comparatively atrophic senescent ovary. The interstitial cells, heavily loaded with lipoids, were normal in structure and apparently in number. Thus a depressed production of follicles and corpora lutea resulting in aging hypoplasia of ovaries seems to be a feature of senescence in these glands. In our breed of rats this change at the age of 20 to 27 months develops only in some animals.

Effects of the Hormones.—In the present experiments on the whole the changes produced in the ovaries of senescent rats to which androgens or oestrogens were administered were the same as or similar to those described in the previous paper (32) and summarised in the review of the literature.

In the previous paper photomicrographs were made from haematoxylin-eosin preparations; in the present paper they have been made from frozen sections stained with sudan-black. The distribution of lipoids in the ovarian elements is important because the sex hormones are steroids. In spite of the fact that sudan-black stains lipoids only, the structure of the ovaries at low magnification is quite distinct (figs. 1 to 7).

Effects of Androgens.—Although on the average the ovaries of "androgenic" rats were smaller ($P < 0.02$-0.01, tables 2 and 3) than in the control rats, in these groups all three stages of androgenic action on the ovaries of senescent rats were present. In the minority of cases there were observed large ovaries showing the first (follicle-stimulating) and second (luteinising) stages; in most cases there were small hypoplastic ovaries (fig. 3). However, even in most of the atrophic ovaries few

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Fig. 1. Control rat. Ovary of approximately normal structure. Ovaries 40 mg.

Fig. 2. Another control rat. Senile atrophy of medium degree: follicles small and few, increased amount of fibrous tissue. Ovaries 37 mg.

Fig. 3. Rat receiving androsterone, oestradiol B.B., progesterone, and thyroid hormone. Androgenic effect overcomes that of the other three hormones. Severe atrophy: no corpora lutea or normal follicles, interstitial cells also very scarce. Stroma elements and fibrous tissue predominate. Ovaries 19 mg.

Fig. 4. Another rat with same treatment as in fig. 3. Partial neutralisation of androgenic atrophy by stimulating action of oestradiol, thyroid, and progesterone. Ovaries 28 mg.

Fig. 5. Rat treated with thyroid hormone only. Stimulating, chiefly luteinising effect. Structure of ovarian elements normal. Ovaries 92 mg.

Fig. 6. Rat injected with oestradiol B.B. only. Slight follicle-stimulating effect, corpora lutea small. Ovaries 44 mg.

Fig. 7. Rat injected with oestradiol and progesterone. Stimulating, chiefly luteinising effect. Normal structure of ovarian elements in comparatively small ovaries of 31 mg.

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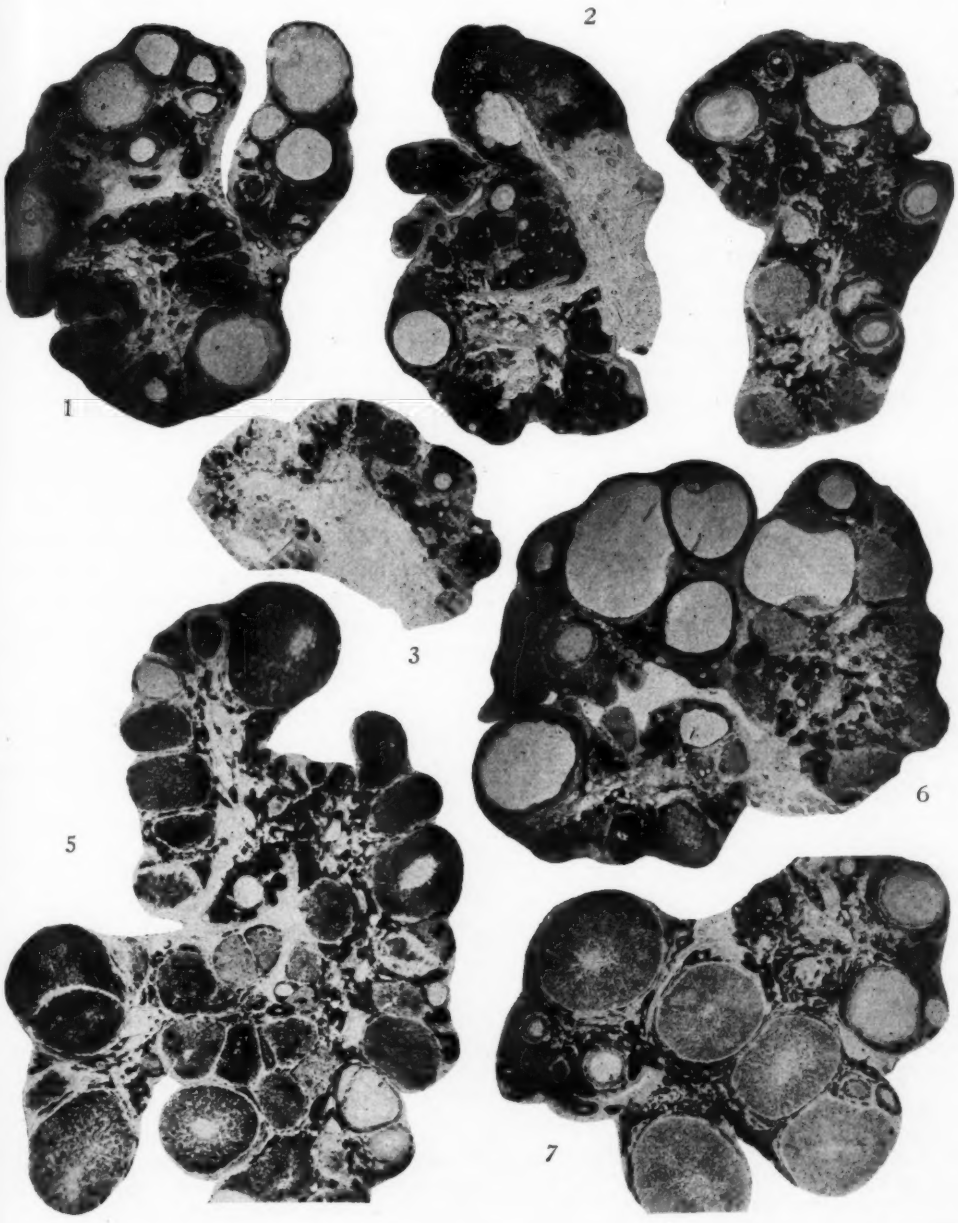

PLATE I

OVARIES, X18, Sudan-Black.

follicles or corpora lutea of normal structure occurred, the greater number of them being of a smaller size. The predominating tissue consisted of stroma elements with atretic follicles, the remnants of degenerated corpora lutea, and interstitial cells poor in lipoids.

Effects of Oestradiol Benzoate Butyrate.—In contrast to the androgen treated animals the majority of the "oestrogenic" rats had ovaries normal in size and structure (tables 2 and 3). Both the first (fig. 6) and second stages of the oestrogenic effects were present. Only in one rat were the ovaries atrophic. These results should be explained by the fact that only a very small nontoxic dose of oestradiol B.B. was used.

Effects of Thyroid Hormone.—As in the previously mentioned experiments (35) larger ovaries were observed in this group ($P < 0.05$, tables 2 and 3). Their histologic structure (fig. 5) was normal, there being numerous normal corpora lutea or follicles (or both) present in various ovaries. Interstitial cells were also normal in appearance and number. Therefore the dose of desiccated thyroid used could be considered a gonadotropic one.

Effects of Progesterone with Oestradiol, Administered Alone or with Thyroid Hormone.—In experiment I the ovaries in these three groups were smaller ($P < 0.05$) than in the control rats, but in experiment II their average weight was the same in the injected and control groups.

The structure of the ovaries varied, being normal (fig. 7) in all rats of experiment II and in about half of the rats of experiment I. In the remaining rats the predominating tissue consisted of interstitial cells, atretic follicles, and connective and vascular tissues; in this stroma, however, comparatively few normal corpora lutea were incorporated with a very few follicles. Thus in the ovaries of the minority of rats in this group the rate of production of follicles and their conversion into corpora lutea was much slowed down as was previously recorded in the case of the majority of the androgenic ovaries.

Effects of Testosterone Propionate or Androsterone Administered Together with Three Other Hormones.—In both experiments the ovaries in these groups were smaller than in the control rats ($P < 0.05$-0.01). Although with both hormonal combinations the structure of these glands was hypoplastic, being the same as that found in rats injected only with androgens, with the androsterone combination a larger number of rats had ovaries with more numerous but small corpora lutea and follicles, as shown in figure 4. In some ovaries the interstitial cells were well preserved, while in others they were greatly decreased in number (fig. 3).

Thus in these groups the stimulating action of oestradiol and thyroid hormones neutralised the depressing androgenic effects only partially or not at all.

Uterus

Features of Aging.—Hypoplasia of the uterus, as judged by relative weights, was not present in senescent rats. On the contrary, in some of the rats the uterus was even unusually large, weighing up to 1000 to 1200 mg. In about half of the 17 control rats the uterus was normal not only in weight, but histologically as well.

Fig. 8. Rat injected with androsterone. Atrophic uterus, 314 mg.

Fig. 9. Rat injected with oestradiol B.B. Uterus no different from those which preserved approximately normal structure in some senescent rats. Uterus, 570 mg.

Fig. 10. Rat treated with testosterone propionate. Gigantic uterus, with cystic hyperplasia of the glands. Infiltration with lymphocytes and leucocytes around lumen, in and around some glands. Slight lace-like foldings of mucosa (progestational effect). Uterus 837 mg.

Fig. 11. Rat treated with testosterone propionate progesterone, oestradiol B.B., and thyroid hormone Gigantic uterus as in fig. 3, but with partial neu tralisation of the pathologic changes. Uterus 1040 mg

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PLATE II

HORN OF UTERUS. X25, Transverse Sections, Haematoxylin + Eosin.

In 9 rats, however, the uterine mucosa was fibrous, in 6 rats a slight or medium degree of cystic hyperplasia of the uterine glands occurred, in 7 rats there was lymphocytic or leucocytic infiltration of the uterine glands or of the periluminar submucosa, and in 1 rat squamous metaplasia was present.

If confirmed on a larger number of senescent and senile rats, fibrous mucosa and other pathologic changes might be considered as features of aging.

Effects of Androgens.—The effect of androsterone is altogether different from that of testosterone propionate, since the former depresses the gonadotrophic secretion of the hypophysis while the latter, besides having the same effect, stimulates the development of the uterus directly and strongly. Therefore, although in both cases the ovaries become atrophic through depression of the hypophysis, the uterus of androsterone rats atrophies ($P < 0.02$) while that of testosterone rats hypertrophies into a gigantic organ ($P < 0.02$-0.01).

Histologically, simple atrophy of all layers is present in the androsterone uterus (fig. 8). In the testosterone uterus, besides hypertrophy of all layers including that of the myometrium cells, the epithelial layer, alone or with a submucosa, makes slight foldings (fig. 10), which indicates a progestational effect of testosterone compounds as described and illustrated in the previous paper (29). There are also some other, definitely pathologic, changes—cystic hyperplasia of the uterine glands, and periluminar and periglandular infiltration with lymphocytes and leucocytes, which are also often present in the glands themselves.

Photomicrographs of these gigantic uteri, less pathologically changed, were given in the previous paper (29, figs. 55 and 56). Except for the high degree of hypertrophy produced, in their structure they were also similar to the uteri of ovariectomised rats treated with the same hormone (29).

Effects of Oestradiol or Thyroid Hormone Administered Alone or Together.—With the doses used the effect of these hormones did not produce any constant or definite changes, the uterus remaining similar to that in the control rats. Therefore figure 9 might illustrate any of these 4 groups and can be taken for comparison with the other figures as a control uterus of normal structure although it was taken from an oestradiol rat. In all the treated groups the same pathologic changes appeared as in the control rats except that there was no squamous metaplasia of the uterine epithelium.

Effects of Oestradiol B.B. with Progestrone, with or Without Thyroid Hormone.—In these two groups the uterus was similar to that of the control rats, but the uterine epithelium and submucosa were slightly indented around the luminar edge. This progestational effect was much less pronounced than in the ovariectomised rats (38, figs. 1 and 2), and the squamous metaplasia of the uterine epithelium was also absent in these groups.

Apparently with the doses used typical progestational and metaplastic changes are more difficult to produce in the normal than in the ovariectomised animals. However, using very large doses of progesterone Selye (51) obtained typical progestational changes.

Effects of Testosterone Propionate Administered Simultaneously with Oestradiol B.B., Progesterone, and Thyroid Hormone.—The gigantic uterus ($P < 0.001$) is even larger than when treated with testosterone alone (tables 2 and 3). Histologically it is similar to the latter with the exception that pathologic changes, cystic hyperplasia of the uterine glands, and cellular infiltration of the mucosa were less pronounced (fig. 11) or were even practically absent. This indicates some neutralisation of the testosterone damaging effects by the remaining three hormones.

Effects of Androsterone Administered Together with Three Other Hormones.—If, instead of testosterone in the four hormonal combination used, androsterone is given, the weight and size of the uterus might remain similar to those of the control rats (table 2), or be decreased ($P < 0.02$, table 3). That some

neutralisation of the androgenic depressing effect on the uterus occurs also in this combination, is shown by the fact that the weight of the uterus remains normal, or in any case there is less reduction than with androsterone alone.

Histologically as compared with the control rats a more cellular mucosa and a more hypertrophied myometrium were observed.

Vagina

Features of Aging.—As judged by relative weights (table 1) or histologic examination, no definite features of aging were observed in the vagina of the control animals.

Effects of the Hormones.—In experiment I the vagina was significantly ($P < 0.05$-0.01) hypertrophied in all the treated groups except those injected with oestradiol alone. In experiment II, however, statistically significant hypertrophy was observed only in the testosterone groups ($P < 0.001$).

Histologically in the thyroid hormone group no definite changes were recorded. In the oestradiol group a typical oestrous cornification was present in 5 rats, a dioestrus condition in 5 rats, and mucification of the vaginal epithelium in 1 rat.

In the progesterone with oestradiol groups, with or without the addition of thyroid hormone, the vaginal epithelium was mucified to various degrees up to the pregnancy mucification stage. Thus in this group the progestational effect of progesterone on the vagina was much stronger than on the uterus.

Of the two androgens examined the strongest effect was obtained with testosterone, which caused considerable hypertrophy of the vagina. The basal layer of the vaginal epithelium with both androgens was low narrow columnar, containing little or no mucus. In the "testosterone" vaginas, the mucosa and muscularis layers were considerably hypertrophied.

In the rats receiving progesterone, thyroid hormone, and oestradiol B.B. with testosterone, hypertrophy of the vaginal layers was greater than in the rats treated with the androsterone combination. The vaginal epithelial layer contained large mucified cells similar or identical with those of the pregnancy vagina. In experiment I the progestational mucification of the epithelium, however, was much more pronounced in the combination of four hormones containing androsterone than in that with testosterone.

Adrenals

Features of Aging.—As in our previous investigations (36), in the present experiments relative hypoplasia of aging was observed in the adrenals (table 1, $P < 0.01$). Histologically there was only one abnormality, which, if confirmed on a larger number of senescent and old rats, might be considered as a feature of aging.

In 10 rats out of 17 control animals, in one or two very small areas of the zona glomerulosa the cells were found to be smaller, with pycnotic nuclei. Below and corresponding to these areas, the demarcation zone (either alone, or with the upper, or more rarely, upper and medium parts of the zona fasciculata) had an irregular arrangement of cells, in most of which the granular cytoplasm was coalescent and the nuclei were decreased in number and size. The cytoplasm was as rich in lipoids as that of the surrounding normal fasciculata cells. In some of these minute apparently degenerated areas, places of regeneration were observed both in the zona glomerulosa and the zona fasciculata. Mitoses were found in the adrenals of the young animals but not in the senescent animals.

Effects of Hormones.—The action of hormone administration on the actual and relative weights of the adrenals of normal senescent rats (tables 2, 3, and 4) was similar in the normal senescent rats and the ovariectomised animals (36, 37, 38), but in most of the senescent groups it was less pronounced.

Thus androgens produced hypoplasia of adrenals ($P < 0.001$), while thyroid hormone slightly enlarged them, significantly in experiment II ($P < 0.05$).

Oestradiol, with the small dose used, alone or with progesterone, had no effect, but with the addition of thyroid hormone there was a significant increase ($P < 0.01$) in the weight of the adrenals.

When all four hormones were injected simultaneously, neutralisation of the hypoplastic action of androgens was produced by oestrogenic and thyroid hormones. The effect of the latter hormones, with androsterone combination, even predominated in experiment I, producing significant ($P < 0.02$) hypertrophy of the adrenals.

Measurement of the adrenal zones in experiment II (table 5) showed corresponding and statistically significant changes in the whole cortex, and in particular in the z. fasciculata, but only after the administration of androgens, alone or in combinations, ($P < 0.02$-0.01) of thyroid hormone alone, or of thyroid together with oestradiol ($P < 0.05$). The size of the fasciculata cells was also significantly smaller ($P < 0.01$-0.001) in the androgenic groups and larger after administration of thyroid hormone with oestradiol ($P < 0.02$).

Histologic structure of the adrenals showed changes similar to those observed after administration of the respective hormones or their combinations to ovariectomised rats (37, 38). Thus androgens produced hypoplasia of the cells and their nuclei (fig. 13) and partial depletion of lipoids. The demarcation zone (a very narrow strip of cells between z. glomerulosa and z. fasciculata) was definitely larger in the androsterone group, and in most rats of the testosterone group.

Although in the other groups measurement of the size of cells (table 5) showed no significant changes, histologic examination of the sections showed enlarged fasciculata cells in most rats of the group injected simultaneously with androsterone and three other hormones (fig. 14).

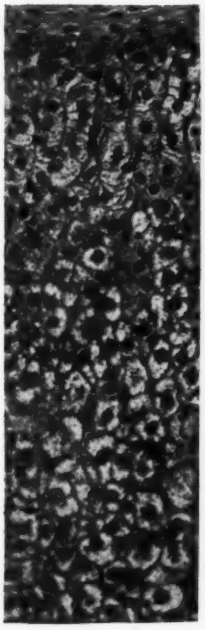
The changes in the glomerulosa and demarcation zones and in the upper part of the fasciculata zone of the rats injected with testosterone propionate simultaneously with three other hormones are shown in figure 15.

With the exception of the previously mentioned androgenic groups, impregnation with lipoids of the fasciculata and reticularis cells was normal or (testosterone combinations) slightly reduced in all the remaining groups. For example, vacuolation of these cells, pronounced in figure 14, slightly reduced in figure 15, and considerably reduced in figure 13, illustrates well the varying degrees of lipoid impregnation in the respective groups. In a few rats receiving oestradiol alone, or in combination with other hormones, the z. glomerulosa was more or less depleted of lipoid granules (figs. 14 and 15). For economy of space the photomicrographs of sudan stained sections are not given.

The degenerative changes in the glomerulosa, demarcation, and fasciculata zones, which were mentioned as being possible features of the aging adrenal, were present in both experiments, as in the controls, in about the same percentage (50 to 67 per cent) in all the treated groups except the groups injected with testosterone alone (43 per cent) or with all four hormones simultaneously. With testosterone combination of four hormones they were present in about 25 per cent, and with androsterone combination in about 44 per cent.

In one rat of experiment I and in one of experiment II, both in the testosterone group, an interesting adenoma-like structure occurred in the adrenals (fig. 16). It consisted of very large cells, with large vesicular nuclei and eosinophilic cytoplasm. These cells were comparatively sharply separated from the ordinary fasciculata and reticularis cells, but originated and were abruptly transformed from these cells with very few intermediate forms. The whole structure was not separated from the normal tissue by any capsule.

Except for the previously mentioned pathologic features, on the whole the changes with the administration of hormones in the adrenals of senescent normal rats were similar, but for some hormones (oestradiol and thyroid) weaker than the changes previously described (37, 38) in ovariectomised animals treated with the same hormones or their combinations.



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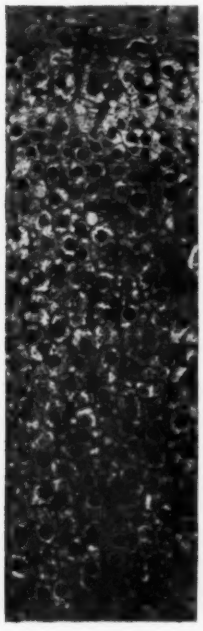

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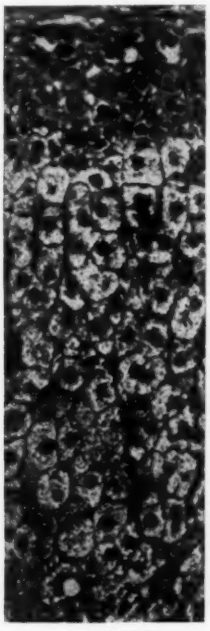

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PLATE III

ADRENAL CORTEX. Haematoxylin + Eosin.

FIGS. 12-15. Part of outer region of adrenal cortex consisting (from top to bottom) of fibrous capsule, z. glomerulosa, demarcation z., and upper part of z. fasciculata. X310.

FIG. 12. Control rat. Adrenals 53 mg.

FIG. 13. Rat injected with androsterone. Z. glomerulosa narrower, demarcation z. wider, cells and several nuclei in z. fasciculata smaller. Decreased vacuolation (lipoid depletion). Adrenals 37 mg.

FIG. 14. Rat injected with androsterone, oestradiol, progesterone, and thyroid hormone. Neutralising effect of oestradiol and thyroid hormone on androgenic atrophying action: fasciculata cells larger than in fig. 13 and even slightly larger than in fig. 12. Pronounced vacuolation (good lipoid impregnation). Adrenals 58 mg.

FIG. 15. Rat injected with testosterone propionate oestradiol, progesterone, and thyroid hormone. The same neutralising effect, as in fig. 14, of oestradiol and thyroid hormone on atrophying androgenic action. Adrenals 79 mg.

FIG. 16. Adenoma-like structure of adrenal cortex, ovoid in form, occupying nearly whole width of the transverse section of the cortex and separated from medulla by a thin layer of reticularis cords. At top and bottom normal adrenal zones, the cords and the cells of which are much narrower than those of adenoma-like structure. Rat injected with testosterone propionate. Adrenals 40 mg. X45.

THYROID

Features of Aging.—Histologically in the young rats the thyroid was active, with high epithelium, little or medium amount of colloid, and some mitoses (4.1 in a standard area).

In senescent normal rats a definite relative hypoplasia of the gland was recorded (table 1, $P < 0.001$). In most cases, it was in a resting condition, with low, mostly cubical epithelium and a considerable amount of hard colloid in the follicles (fig. 17). In 3 rats out of 17, however, the gland was moderately active with a higher epithelium and less colloid (fig. 18). No mitoses were found. Two definitely pathologic changes were found in 3 rats (in one rat a small clump of metaplasia of thyroid epithelium and in two rats sclerosis of the thyroid).

If confirmed on a larger number of senescent rats, these changes could be considered as features of aging in the thyroid of rat and in true senility they might become more pronounced or more frequent. Thus Fischer (13) described an adenoma and an adeno-carcinoma in the thyroid of 2 old rats.

In human old age both atrophic thyroids with sclerosis and hyperplastic thyroids have been observed. Dogliotti and Nutti (9) believe that hyperplastic thyroids are typical of cases of true senility, while atrophic ones are typical of senile patients dying from exhausting or infectious diseases.

Effects of Hormones.—The changes in the actual and relative weights of the thyroid, in most cases an increase, were statistically not significant except in the testosterone group of experiment I ($P < 0.02$). Without histologic examination, however, these changes alone cannot explain changes in the function of the gland, since for example its increase might be caused by accumulation of colloid (depressed function), or by hypertrophy of the cells and hyperplasia of the follicles, as in the present experiment I in the groups mentioned subsequently (stimulated function).

Histologic investigation showed some definite changes similar to those previously described (37, 38) in ovariectomised rats after administration of the same hormones or their combinations.

Thus the gland was stimulated especially strongly by testosterone, to a lesser degree by androsterone, and less regularly by oestradiol alone or with progesterone (figs. 19-22). Alexiu (1) also obtained stimulation of the thyroid after injections of oestradiol or progesterone into normal female rats.

Thyroid hormone, on the contrary, alone or with oestradiol, depressed the thyroid gland.

When all four hormones were injected simultaneously the depressing effect of thyroid hormone on the thyroid gland predominated in most cases (fig. 24). In a minority of cases, however, the stimulating effect of androgens, oestradiol, and progesterone more or less neutralised the depressing effect of the thyroid hormone (fig. 23).

In none of the treated rats were sclerotic changes found in the thyroid.

A pathologic overstimulation in the form of epithelial metaplasia was observed more fre-

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FIG. 17. Control rat. Resting type of thyroid present in majority of control senescent rats: low epithelium and considerable amount of hard colloid in most follicles. Thyroid 27 mg.

FIG. 18. Control rat. Moderately active thyroid found only rarely in senescent rats but usually in adult rats: higher epithelium and less colloid in most follicles. Thyroid 19 mg.

FIGS. 19-22. Rats receiving testosterone propionate, androsterone, oestradiol B.B., and progesterone with oestradiol, respectively. Stimulating action of these hormones on senescent thyroid. Active glands, with high epithelium and comparatively less colloid. Respective weights 20, 22, 20, and 21 mg.

FIG. 23. Rat treated with androsterone, oestradiol, progesterone, and thyroid hormone. Depressing effect of thyroid hormones partly neutralised by other hormones. Active thyroid, 23 mg.

FIG. 24. Rat treated with testosterone propionate, oestradiol B.B., progesterone, and thyroid hormone. Stimulating hormones failed to neutralise depressing effect of thyroid hormone. Thyroid 24 mg. Both types, as in figs. 23 and 24, were present in senescent rats treated with four hormones simultaneously.

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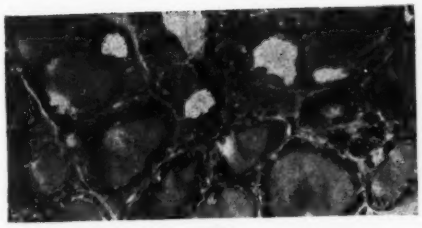

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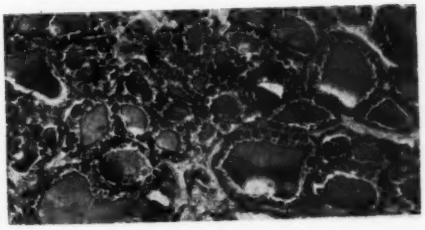

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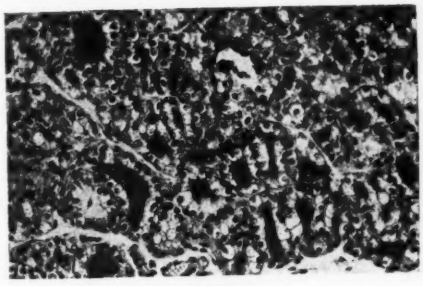

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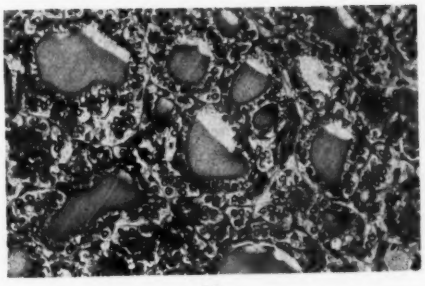

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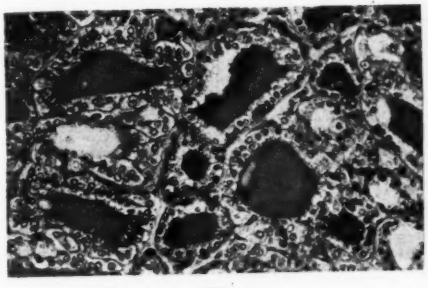

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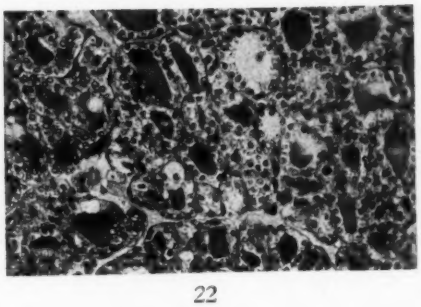

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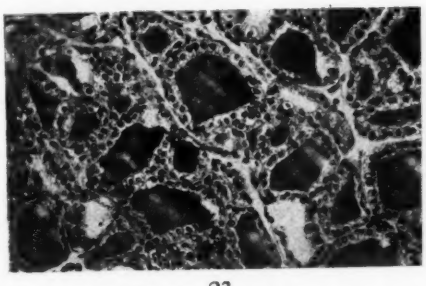

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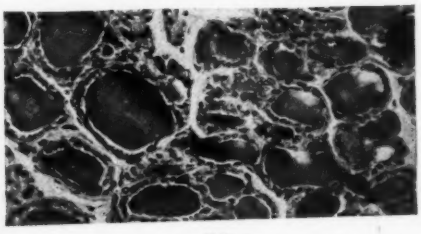

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PLATE IV

THYROID. X180, Haematoxylin + Eosin.

quently in the rats injected with the stimulating compounds in the androgenic, oestrogenic, and progesterone + oestradiol groups. This metaplasia in 4 cases developed into adenomas, in 2 rats affecting the whole thyroid gland (fig. 25). The histologic structure of these adenomas at higher magnification as seen in figure 26 resembled trabecular benign adenomas as described by Means (44, p. 124) and Crotti (7, pp. 258, 259). Burrows (4) produced an adenoma of the thyroid similar in structure to that observed in our rats by prolonged administration of oestradiol to a mouse.

Parathyroids

While in the parathyroids of young rats many mitoses were present, in those of senescent control animals they were absent. At the same time the amount of fibrous tissue was slightly greater in the parathyroids of most of the control rats.

A considerably increased development of fibrous tissue was found in the glands of 4 animals only, namely in 1 control rat and in 3 rats injected with all four hormones simultaneously. In the control rat the structure of the parathyroid epithelium seemed to be normal. In the treated animals most glandular cells were atrophic, containing a decreased amount of cytoplasm, darkly stained with haematoxylin, and pycnotic nuclei. Several groups and cords of cells seemed to be compressed and strangulated by fibrous tissue, producing a typical picture of sclerosis in the organ (fig. 28). A small number of dark haematoxylinophilic cells might occur normally in the rat parathyroid. Their presence, however, in such large numbers and in such an atrophic and degenerated condition was a definite pathologic change in the treated animals.

With the mixture of hormones containing testosterone (2 rats) these changes were more pronounced than with the androsterone combination (1 rat).

In one rat having thyroid adenoma the simultaneous injection of progesterone, oestradiol, and thyroid hormone produced an adenoma-like structure of the parathyroid also (figs. 25, 27). It consisted of ribbons of comparatively little changed parathyroid cells, among which were nests of large cells with cytoplasm lightly stained with eosin and large vesicular nuclei similar to some of the thyroid-adenoma cells.

Thymus

Features of Aging.—Involution of the thymus with aging, starting from the period of sexual maturity, has repeatedly been recorded both in human beings and animals by several authors. The literature on the subject and

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Fig. 25. Rat treated with progesterone, oestradiol B.B., and thyroid hormone. Adenoma has transformed nearly the whole thyroid, leaving normal structure of the gland only in a narrow strip at the top and right hand side of the photograph and a few occasional, more or less normal, follicles (recognised by dark colloid content) dispersed in the mass of the adenoma tissue. On the left side of the photograph, marked by a dotted line, is an adenoma of parathyroid, recognised by its ovoid form and stripes of dark cells and separated from thyroid adenoma by a fibrous capsule. Thyroid 26 mg. X24.

Figs. 26 & 26A. The same thyroid adenoma as in fig. 25 but magnification is X140. Its histologic structure varies considerably even in closely neighbouring parts of the adenoma, forming acini of larger epithelial cells, with larger and more vesicular nuclei than those of normal thyroid epithelium. At the top of photograph adenoma cells become loose and invade stroma (fig. 26) or (fig. 26A) the cells become more typical of sarcoma, spindle-shaped, with oblong nuclei, invading interacinar spaces.

Fig. 27. Adenoma of parathyroid, the same as in fig. 25, but magnification X140. At the bottom are curved ribbons of normal parathyroid cells with small nuclei, abruptly transformed into two kinds of adenoma cells; reticulum of dark cells, similar to normal cells, in meshes of which are large light cells with large nuclei. These two kinds of cells might correspond to the two kinds of normal parathyroid cells in the rat, the lighter, of which the gland usually consists, and the darker, which normally are found more rarely in the gland.

Fig. 28. Sclerosis of parathyroid. Rat treated with testosterone propionate, oestradiol B.B., progesterone, and thyroid hormone. X64. →

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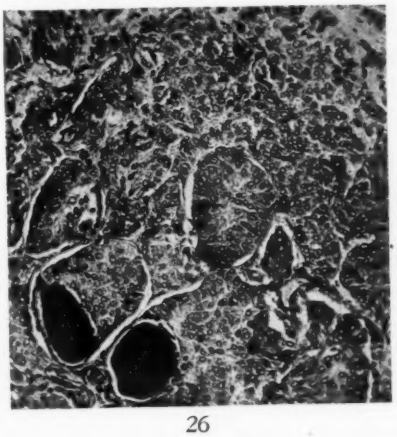

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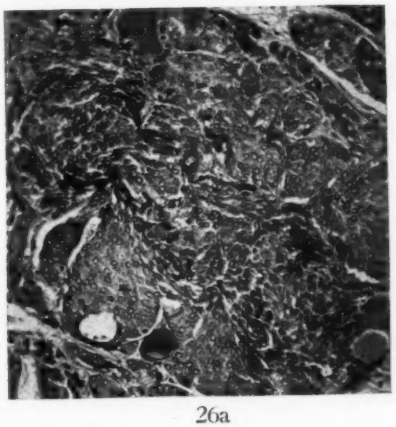

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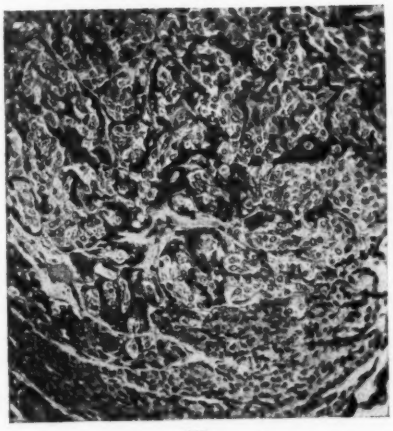

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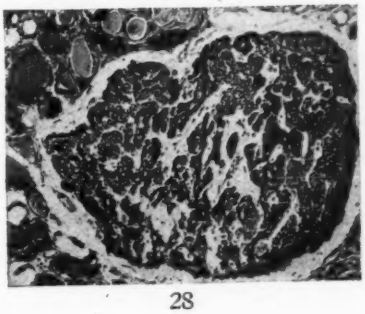

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PLATE V

THYROID AND PARATHYROID. Haematoxylin + Eosin.

their own observations on rats have previously been given by Ross and Korenchevsky (50).

The results of the present experiments confirm the previous ones: in untreated control rats a considerable atrophy of the thymus was found (table 1), histologically demonstrated by decrease of the lobules, thinning of the thymocytes in the parenchyma, and increase of fat and fibrous tissues between the lobules. Mitoses, which were abundant in the thymus of the young animals, were absent in the intact senescent rats. In addition, in about one-third of these rats small nests of epithelial cells were found, the growth of which seemed to commence and proceed from the reticular epithelial cells of the thymic stroma.

Thus as in the case of adenoma-like structures in other organs observed in our rats and described previously, the thymus structures represent metaplasias of the epithelial cells of the organ. In size and structure these hyperplastic epithelial nests were also similar to those found in the previous experiments in untreated adult and senile rats (50, fig. 7). In all cases except one they consisted of very small clumps or ribbons of epithelial cells, solid in structure, i e., without lumen. In one case, however, the structure was a little larger, with a few groups of cells in follicular arrangement, and there were a few small cysts. The latter picture in our rats, as will be shown in the following, was often found in and was more typical for treated rats.

The best description of these epithelial structures in different animals has been given by Cowdry (6).

Effects of Hormones.—In previous investigations on ovariectomised rats (50) it was found that androgenic and oestrogenic hormones in comparatively large doses decreased considerably the weight of the thymus by hastening its involution. In rats injected with oestradiol dipropionate in weekly doses of 0.018 to 0.09 mg. epithelial structures were produced which were more numerous, larger, and more adenoma-like in their cellular arrangement than those of the control rats. They occurred also in most of the injected animals.

Plagge (46, 47) confirmed these results both on gonadectomised and normal rats, although the structures observed by him were predominately cystic formations. By using massive doses of oestradiol dipropionate (0.1 to 0.2 mg.) for a prolonged period (ten and a half months), Plagge tried to transform these adenoma-like structures into tumours, (carcinomas in particular) but failed.

In the present experiments, a definite decrease of thymus weight was observed in the groups injected with testosterone propionate alone or in combination with other hormones ($P < 0.05$). Histologic investigation, however, showed that in several oestradiol and androsterone rats an increased development of fibrous and fat tissue was responsible for little or no change in the weight of the thymus.

The greatest atrophy of thymic parenchyma was observed in the testosterone groups: in many cases the organ consisted chiefly of fibrous and fat tissue with only small remnants of dispersed groups of thymocytes. In this stroma were observed many, although atrophic, nests and follicles of epithelial cells. Apparently in their growth these adenoma-like structures were also strangulated by the increased development of fibrous and fat tissues. Histologically, as compared with the testosterone groups, atrophy of the thymic parenchyma was considerably less pronounced in the androsterone and oestradiol groups.

In the progesterone + oestradiol group the thymus was about equal to that of the control rats. In the groups treated with thyroid hormone alone or in combination with oestradiol there was observed not only an absence of atrophy of thymocytic parenchyma but on the contrary somewhat better preservation of normal structure.

Hyperplastic epithelial structures in the groups injected with oestradiol, testosterone, or with progesterone and oestradiol simultaneously were found in about the same number of rats (35 to 44 per cent) as in the control groups. In the groups to which thyroid hormone alone or in combination with other hormones was administered, the number of these

structures was increased, being present in about 63 to 66 per cent of the animals. It is remarkable, however, that in not one thymus of the rats injected with androsterone alone were these formations found.

The largest structures, however, occurred in the group treated with thyroid hormone + oestradiol, and in the rats to which androsterone + three other hormones were administered simultaneously. In some of them it seemed that the adenoma-like structure invades into and eliminates normal thymocytic parenchyma. In 2 rats nearly one-third of the thymus was replaced by this adenoma-like growth, the size of which was at least twenty times larger than the largest structure in the control rats.

Medium size structures have been observed in the groups treated with oestradiol alone or together with progesterone and in the group treated with thyroid hormone alone.

Thus it is possible to conclude that most of the hormones injected, especially in two combinations, increased the number, size, or both, of the adenoma-like structures in the thymus of senescent rats.

Liver

Features of Aging.—As in the previous investigations, typical relative aging hypoplasia of the liver was also developed considerably (table 1, $P < 0.01$) in the present experiments. In the old rats the number of the liver cells with large nuclei (2.8 per cent) was smaller than that in the young rats (7.3 per cent, $P < 0.02$), and the ratio of cytoplasm to nucleus was larger than in the young rats (9.9 and 7.6 respectively). This difference, however, was statistically not significant ($P > 0.05$). The average size of the liver cells in old (7.43 mg.) and young (7.53 mg.) rats was about the same, although the percentage of large cells was larger in young rats (11.3 and 13.5 per cent respectively, $P > 0.05$). All these measurements were made by the paper replicas method.

Histologically, two abnormal changes were found. In about 18 per cent of the control rats (table 6) a slight hyperplasia of the bile ducts was observed in the form of minute clumps, one or two of them on the cross section of a small liver lobe. They were always very small in size, being typically represented in figure 30. None were found in the young rats.

It is well known that, in regeneration of the liver, hyperplasia of the bile ducts is observed regularly. The literature on the subject was well reviewed by Fishback (12). Opinions are divided only on the question of whether or not true liver cells could be developed from these regenerating duct cells. It is also well known that liver adenomas can originate from and consist of bile ducts (21, 58, 59). Herxheimer (21, p. 813), however, separates into a group of pseudoadenomas those cases in which the adenoma-appearing structures consist of very minute knots of ducts. He explains their origin and development not by tumour-producing causes but by the usual regenerative process occurring in those small liver areas which were degenerated or destroyed by some toxic agent such as bacterial.

Therefore, in our untreated senescent rats these minute hyperplasias as observed in the control rats might fit the Herxheimer theory, since in senescence and old age various damaging factors (e. g., auto-intoxications) are in operation in the organism. The appearance of these hyperplasias only in some of the senescent animals might be explained by the varying rate of aging.

The second pathologic change consisted of very small nests of round cell infiltrations around the hepatic blood vessels present in about 35 per cent of the control rats. In the young rats, however, these infiltrations were also present but they were less numerous.

Mitoses, numerous (283 in a standard area) in the liver of the young rats, were present in small numbers only (table 6) in senescent control rats (5.7-9.8 in a standard area).

Effects of Hormones.—In experiment II, in which the doses were adjusted more correctly, the changes in actual weights of the liver were more pronounced than in experi-

ment I. In experiment II they were statistically significant only in groups of rats treated with all four hormones simultaneously. The hypertrophy obtained in the combination containing androsterone ($P < 0.01$) was more pronounced than in that with testosterone propionate ($P < 0.05$), the relative fat-free weights being statistically significant only in the former combination. This fact should be explained chiefly by the greater fat deposition in the body of these rats.

In experiment I there was only one group which showed a statistically significant hypertrophy of the liver, the rats treated with progesterone, oestradiol, and thyroid hormone ($P < 0.01$). Probably the combination with

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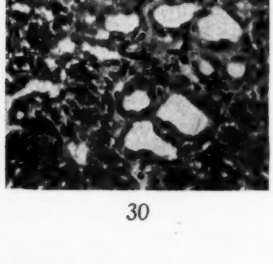

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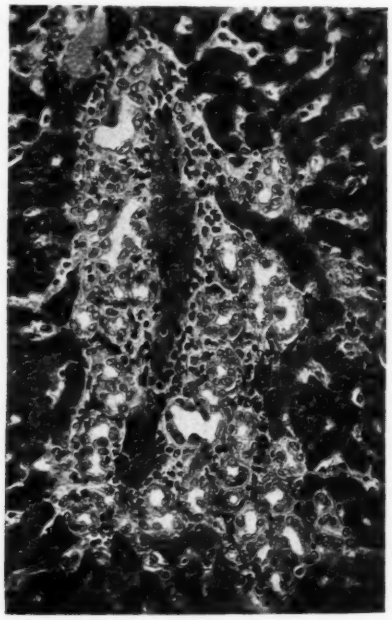

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PLATE VI

HEPATIC ADENOMA-LIKE STRUCTURES. Haematoxylin + Eosin.

FIG. 29. Rat injected with oestradiol B.B. Transverse section of about half a small liver lobule with many adenoma-like structures of various sizes (light areas containing small follicles of adenoma-like tissue). X24.

FIG. 30. Control senescent rat. Hyperplasia of bile ducts, small in size, with few follicles lined with flat epithelium with oblong nuclei and comparatively thick septa of connective tissue. X225.

FIG. 31. Rat treated with thyroid hormone. One of the small adenoma-like structures developed around blood vessel, apparently starting an ingrowth (on right side) into normal liver tissue. As compared with fig. 30, cells, and nuclei are larger. Septa between follicles very thin. Nuclei vary in size and shape. X225.

testosterone was too strong and toxic and with androsterone it was too weak.

There was a remarkable difference in the number of mitoses between experiments I and II (table 6): while in the first experiment the number of mitoses was increased considerably (with a statistical significance $P < 0.05$-0.01 in all treated groups except in progesterone + oestradiol and testosterone groups), in the second experiment it was so only in the group of rats treated with thyroid hormone.

Such a difference, being contradictory to the changes in liver weights, suggests that hyperplasia of the cells was accomplished by the end of experiment II and for some reason was delayed in experiment I.

Measurement of the cells, performed only in experiment II, did not show any statistically significant changes. The percentage of large nuclei, however, was significantly ($P < 0.05$-0.02) increased in all groups except the oestradiol, testosterone, and oestradiol + progesterone groups (table 6).

All the previously mentioned data indicate that a true, statistically significant hypertrophy of the liver was obtained in the groups injected with combinations of hormones and that this hypertrophy was most probably due chiefly to hyperplasia and not hypertrophy of the liver cells. However, in a minority of the rats belonging to these groups definite hypertrophy of cells was observed in photomicrographs.

In contrast to these apparently favourable results, histologic investigation revealed simultaneous pathologic changes in some of the treated rats.

Thus bile duct hyperplasia was observed in a greater number of the experimental rats (table 6); and in 2 animals was developed to such an extent that it resembled adenoma formation (fig. 29). One of the rats with these structures belonged to the oestradiol group, and the other to the thyroid hormone group.

The greatest frequency of bile duct hyperplasia occurred (table 6) in the rats to which was administered thyroid hormone alone, in combination with oestradiol, or with oestradiol + progesterone. In the control rats these hyperplasias were a conglomeration of a few ducts lined with a flat epithelium and separated from each other by comparatively thick septa of connective tissue (fig. 30).

As compared with these controls, in some of the treated rats the adenoma-like conglomerations were not only bigger but also of a more compact structure, consisting of a much greater number of ducts separated from each other by thin septa. The epithelial cells of the ducts were larger in size (fig. 31). Enhancement and transformation of the hyperplasias into the adenoma-like structures were probably caused by overstimulation with too large doses of the hormones used.

Previously (33, 35) a review of the literature on the subject was made, and our own experiments on the effects of comparatively large doses of thyroid hormone were described. These doses were well tolerated by the rats, since the animals were not only kept on a diet rich in vitamins but also they were comparatively young (150 days). No adenoma-like structures were observed in the livers of these rats, but in one out of 20 treated rats a minute clump of ducts was found similar to that observed in the control senescent rats.

It is possible that the adenoma-like structures were produced by much smaller doses of thyroid and other hormones in the present experiments because the rats were senescent animals.

Round cell infiltrations in the liver of the treated rats were found in about the same percentage (31 per cent) as in the control untreated rats (35 per cent).

Kidneys

Features of Aging.—As in our previous experiments, a definite ($P < 0.001$) aging relative hypoplasia of the kidneys was observed (table 1). In young rats the number of mitoses in a standard area was much larger than in the old control rats (42.3 and 1.1 respectively). There was, however, no statistically significant difference ($P > 0.05$) in the size of the tubules (7.1 and 7.3 mg. respectively) and their lumina (1.0 and 0.8

mg. respectively), as measured by the paper replicas method.

Histologically in about 53 per cent of the control rats, round cell infiltrations, minute in size and very few in number, were found around some blood vessels. Although fewer in number, these infiltrations were present also in some of the young rats. Other pathologic changes, oedema of glomeruli and hyaline casts, were present in about 41 per cent of the control rats. When they were observed there were usually only one or two oedematous glomeruli and casts found in some of the cross sections of the kidney. None were found in the young rats.

Thus these abnormalities, both very slight in degree of development and present only in a part of the animals, might be connected with the processes of aging in rat kidneys.

Effects of Hormones.—Statistically significant ($P < 0.05$-0.001) hypertrophy of the kidneys, as judged by their increased actual weight, was observed in the rats treated with testosterone propionate (but not with androsterone), desiccated thyroid, and, in a greater degree, after the simultaneous administration of three or four hormones (tables 2-3).

However, when the calculations were made on the basis of fat free body weight (table 4), these changes were less pronounced ($P < 0.05$), or statistically not significant, due chiefly to varying fat deposition in different groups (tables 2-3).

The true character of hypertrophy of the kidneys in the previously mentioned groups was confirmed by the larger size of their tubules ($P < 0.05$-0.001) as measured by paper replicas (table 7). Tubular lumina were also slightly enlarged in groups treated with testosterone propionate and after simultaneous administration of all four hormones. The number of mitoses (table 7) and the variation in different groups was small and not significant statistically.

In the same table the occurrence of the pathologic changes in various groups was expressed by percentage figures. Because of the small number of rats in each group, these percentage variations might be considered only as an indication of the general tendency towards increase or decrease of the changes observed.

Thus the round cell infiltrations were considerably decreased in number in the testosterone group (13 per cent) and in the groups treated simultaneously with thyroid hormone and oestradiol, without or with progesterone (17 per cent).

Occurrence of oedema in glomeruli and the hyaline casts were also decreased in the testosterone group (19 per cent). Contrastingly, in the rats treated with oestradiol plus thyroid hormone simultaneously, oedematous glomeruli occurred considerably more often (83 per cent). In the other groups the changes in these values were comparatively small and not significant.

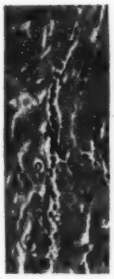
Therefore a definite improvement of pathologic senescent changes in the kidneys apparently occurred only after administration of testosterone propionate.

The results were similar to those obtained in the previously published investigations on the effects of the same hormones on ovariectomised rats (22, 36, 38, 39) and on normal intact young animals (27, 28, 53, 54).

Heart

Features of Aging.—A comparison of the respective figures in table 1 shows a definite aging relative hypoplasia of the heart in untreated senescent rats ($P < 0.001$). This hypoplasia was not noticeable in our previous experiments (36) when only a short range of rat's span of life was investigated (61 to 140 days). As was demonstrated in the same paper (pp. 325-326), this hypoplasia was found when the usual (not fat-free) relative weights of the heart were calculated from the actual weights given in the experiments of Freudenberger (14-18) and Donaldson (10).

Histologically in the present experiments, no definite pathologic changes were found in the heart of untreated senescent rats.



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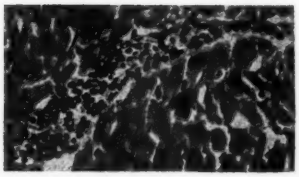

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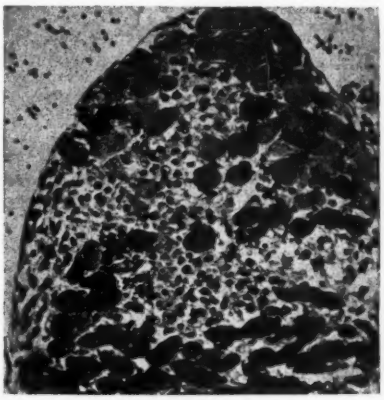

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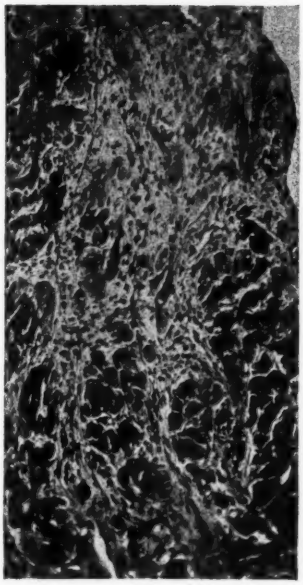

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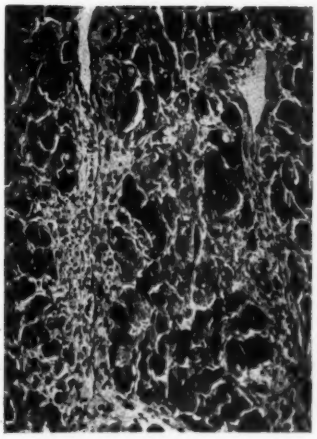

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PLATE VII

HEART. Haematoxylin + Eosin.

FIGS. 32-33. Rats treated with testosterone propionate. Beginning of myocardial lesions: accumulation of round cells in and alongside of small blood-vessels (fig. 32); and next stage, their accumulation into small nests. X225.

FIG. 34. Rat treated with testosterone propionate, oestradiol B.B., progesterone, and thyroid hormone. Transverse section of one of the heart papillae. Infiltration between cardiac fibres of numerous Aschoff's cells (with larger vesicular nuclei of uneven shape) and comparatively few lymphocytes. X225.

FIG. 35. Rat treated as in fig. 34. One of the last stages of development of cardiac lesions: formation of fibrous scar, in place of the previous cell infiltrations, in this case starting from endocardium (top right corner). X140.

FIG. 36. The same rat as in fig. 35. Formation of scars, alongside two small blood-vessels, in myocardium. X140.

Our results and recalculations correspond, in general, to the observations of Warthin (60) on senile atrophy of human heart. In his 38 years of pathologic experience, Warthin, out of a great number of autopsies of old persons, could select only 25 cases of death from senility alone. He found that death in all these cases was apparently caused by simple myocardial atrophy and inadequacy. Coronary sclerosis was of a slight degree; in one man in the late nineties it was practically absent. He concludes (p. 148), "the purely senile death should be, therefore, a cardiac death."

Effects of Hormones.—As judged by increase in actual weight, in both the present experiments a statistically significant hypertrophy ($P < 0.05$-0.001) of the heart was obtained after administration of androgens, thyroid hormone, progesterone with oestradiol (but not of oestradiol alone), and combinations of three or four hormones. For the same reason as previously mentioned in relation to other organs, increase in the relative fat-free weight of the heart was less significant ($P < 0.05$-0.02) than that in the respective actual weights; or, in experiment II, this increase in the relative weight of the heart even became statistically not significant in the animals treated with androgens or oestradiol with progesterone.

Estimation of the percentage of large cardiac muscle fibres (as previously described) showed that a statistically significant ($P < 0.05$-0.01) increased number of the hypertrophied fibres occurred in rats after administration of testosterone propionate, thyroid hormone alone or with oestradiol, and all four hormones simultaneously. The respective figures for large fibres were 23, 21, 18, 19, and 22 per cent, as compared with 14 per cent in the control group.

Detailed histologic examination, however, revealed some pathologic changes of various degrees in the following groups: very slight changes after administration of testosterone propionate in 3 rats out of 16, and similarly after thyroid hormone treatment in 3 rats out of 12; both slight and pronounced changes after administration of all four hormones simultaneously in 11 rats out of 32 ($P < 0.001$). None of these changes were found in the control or any other groups.

The changes consisted, when of slight degree, of an increased number of round cells between and alongside some of the cardiac fibres (figs. 32, 33), or of small clumps of these and Aschoff's cells (2, 3) in comparatively few places of the myocardium.

When more pronounced, the infiltration of these cells was present in several places in the myocardium and endocardium and affected comparatively large areas, for example, a whole papilla (fig. 34), or penetrated deeply from the endocardium into the myocardium.

When the process had lasted for a comparatively long time, the cellular infiltrations were gradually transformed into sclerotic changes (fig. 35) with scars of fibrous tissue often developing alongside the myocardial blood vessels (fig. 36). In the same way the cardiac papillae might become fibrous. In other words, various degrees of local myocarditis or, in a few cases, more or less general myocarditis were present.

We could not, however, detect fatty degeneration in the cardiac fibres even in those affected areas in which these fibres were becoming gradually more and more atrophic under the pressure of developing fibrous tissue.

Since more numerous and more pronounced cases of myocarditis occurred in the groups of rats treated with all four hormones simultaneously, hormonal overstimulation could probably be considered as the cause of this pathologic change.

The changes observed have previously been described in experiments with thyroid hormone given in large doses to various animals. The literature on the subject has been well reviewed (45, 61).

In our other experiments (35) high doses of desiccated thyroid (up to 280 mg. six times a week) were given to normal adult rats for a period from 47 to 53 days. These doses were tolerated comparatively well because the animals were kept on a diet rich in vitamins.

In these experiments in about 32 per cent of the treated animals similar more or less pronounced degrees of myocarditis and endocarditis and even pericarditis were obtained (unpublished results).

Histopathologic cardiac changes, also of a similar character, have been described in cases of exophthalmic goitre and some other diseases (particularly in rheumatism) (2, 3).

The best controlled observations on cases of human hyperthyroidism were made by Weller (61) and Rake and Eachern (48). They compared two groups of patients: those who died from hyperthyroidism, complicated as it usually is by some other disease directly causing the death; and control patients, without hyperthyroidism, who died from the same disease which directly caused the death, and who were of the same age and sex. The authors found that in both groups the same histopathologic changes occurred in the heart. In the hyperthyroid patients, however, the cardiac lesions were present more frequently and were of a more severe degree.

These important observations indicate that the histopathologic picture obtained after treatment with thyroid hormone is not a specific one for this hormone but could be produced by various agents.

Spleen

Features of Aging.—Relative hypoplasia of the spleen was very pronounced in senescent rats (table 1, $P < 0.001$). Histologically, however, the only significant change was a decrease in the number of mitoses and of the giant cells. The number of the latter in a standard area was 7.5 in the senescent rats, and 15.1 in the young animals.

There was no difference in the number and size of the Malpighian bodies as measured by paper replicas method (13.3 mg. in the senescent rats and 13.6 mg. in the young animals).

Andrew (1a), examining the spleens of another breed of rats (Wistar Institute), aged 800 to 1170 days (i. e. older than our rats), found considerably more pronounced changes: loss of reaction centres, partial or total destruction of the architecture of the pulp, and a change in red pulp from a predominantly reticular to a predominantly sinusoidal type. The number of pycnotic nuclei was also increased. In old men he found similar changes.

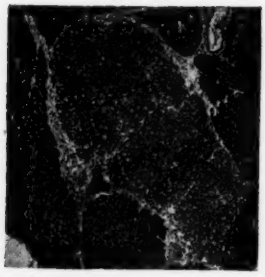
Effects of Hormones.—An increase in actual weight of the spleen was observed in the groups treated with thyroid hormone alone or with oestradiol (statistically not significant); and in the animals to which three or four hormones were administered simultaneously ($P < 0.05$-0.01). As in the case of some other organs and probably for the same reasons, the relative weight of the spleen in these groups was less pronounced; it was statistically significant in only two groups, namely those treated with androgenic and three other hormones simultaneously ($P < 0.05$). Histologically the number of giant cells was increased significantly ($P < 0.01$-0.001) in the groups to which thyroid hormone was administered either alone, or simultaneously with two or three other hormones. The respective numbers of these cells in a standard area were 20, 13, 19, and 19 in the treated groups as compared with 7 in control rats.

The average number and size of Malpighian bodies as measured by paper replicas was apparently increased in most treated groups. For example the respective average figures for control and testosterone groups were 13.3 and 15.7 mg. Statistically, however, the changes were not significant.

The number of mitoses in various groups was not counted, but there was no such obvious difference as could be detected by usual examination of the sections.

Pancreas

Features of Aging.—Andrew (1b), in his careful examination of senile changes in the pancreas of both rats and man, found proliferation of inter- and intralobular ducts, frequently with formation of apparently solid masses of cells, appearance of cyst-like local expan-



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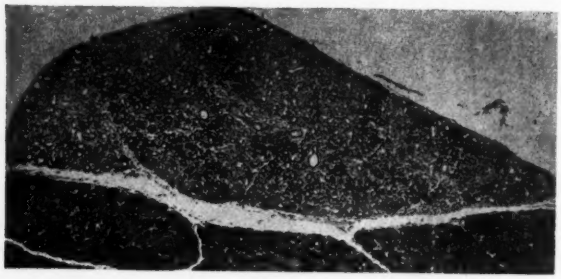

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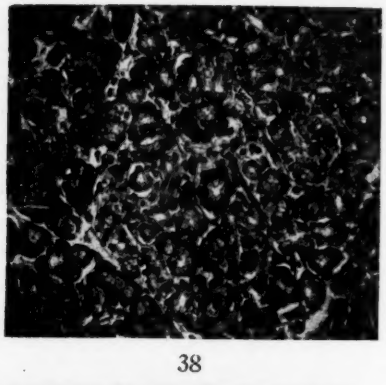

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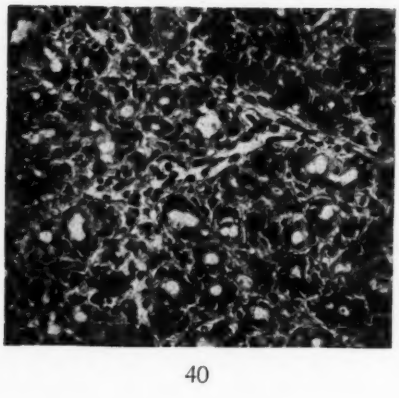

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PLATE VIII

PANCREATIC ADENOMA-LIKE STRUCTURES.

Haematoxylin + Eosin.

FIG. 37. Control senescent rat. Metaplasia of exocrine acini in a small lobule of pancreas, surrounded by normal lobules. X45.

FIG. 38. Same rat. At larger magnification of X225, a small area from metaplastic lobule. Normal exocrine acini on the left, metaplastic acini on the right. In the latter as compared with the former, decrease or disappearance of haematoxylinophilia of outer part of cellular cytoplasm, but zymogen granules distinctly seen. Decrease in size of most acini and slight increase of lumen.

FIG. 39. Rat treated with oestradiol B.B., progesterone, and thyroid hormone. Adenoma-like structure larger than metaplastic area in control rat. Both exocrine acini and those in the structure are larger. X45.

FIG. 40. Same rat. A small area of adenoma-like structure at magnification X225. Considerable disorganisation of several acini with cells becoming loose and invading interacinar spaces. Variation in size of nuclei. Considerably increased lumina. In the middle of the extreme right—one mitosis.

FIG. 41. Rat treated with testosterone propionate. Hypertrophy of normal acini (at the top) as compared with those in control rat (fig. 38, on the left). Just below normal acini is formation of solid clumps of adenoma-like structures from metaplastic acini with great variation in nuclei, and 4 mitoses. X225.

sions of these ducts, and degenerative changes in the endocrine cells.

In the present experiments the weight of the pancreas was not investigated, nor were any cellular measurements made histologically. The usual microscopic examination of the pancreas in 17 control rats showed a pathologic change in only one animal (metaplasia of the exocrine cells in one microscopically small lobule of the pancreas) (figs. 37, 38). The cells and acini became smaller and lost their usual haematoxylinophilia, partly or completely, of the outer part of the cytoplasm, the whole of which was lighter stained with eosin. The acini lost their dented outline, becoming round, and most of them acquired slightly enlarged lumen. No disintegration of the acini nor mitoses were found. Various transitional forms from normal to metaplastic acini were observed.

As compared with aging metaplasia in liver, thyroid, and thymus of normal intact senescent rats as described above, the size of the metaplastic area in the pancreas was considerably larger.

No metaplasias were found in the young rats, nor were there round cell infiltrations around the blood vessels. In senescent rats minute nests of these infiltrations were observed in about a quarter of the animals.

No mitoses in exocrine nor endocrine cells were observed in senescent rats but they were present in exocrine cells of most of the young rats and in one young animal in the Langerhans islands as well.

Effects of Hormones.—In photomicrographs the acini of exocrine pancreatic cells seem to be larger in the injected groups while no definite difference was noted in the Langerhans islands.

Metaplasias were present in all groups except two, namely, one simultaneously treated with progesterone and oestradiol and one treated with thyroid hormone and oestradiol.

In each of the remaining treated groups the number of the rats with metaplasias was from two to four times larger than in the control group. While some of the metaplastic areas were similar in size and structure or even smaller than the one present in the control group, in 7 treated rats they were not only considerably larger but could be defined as adenoma-like structures (figs. 39-41). Thus, in these structures, the size of the cells and their nuclei was variable; some of the acini disintegrated into singular cells invading interacinar spaces, and occasionally forming solid nests. Mitoses were scattered irregularly but in places were numerous (fig. 41).

As in the control rat, some transitional forms of acini were present, with various degrees of transformation of the normal cells into metaplastic ones. One of these structures, consisting of regular small follicles, suggested another source of their origin; namely, in agreement with Andrew from the smallest ducts and, as we suggest, also from those pancreatic ducts which are in touch both with larger normal ducts and the Langerhans islands. Maximow and Bloom (43, p. 453) describe the latter as consisting of undifferentiated cells and taking part in the regeneration of pancreatic tissue. The appearance of this pancreatic structure resembled adenoma-like hyperplasia of the smallest bile ducts, which has been described previously and illustrated by figure 31.

Round cell infiltrations were also present in pancreata of the treated rats, in quantity and quality not differing from those which have been described in the control senescent rats.

Brain

Features of Aging.—Decrease in relative weight of the brain with aging is a very striking feature (table 1). Literature on the subject has been reviewed previously (23). The mechanism of development of this hypoplasia however, is different from that observed in other organs.

As is well known the human brain is morphologically fully developed by the end of the first year of life, and after this period mitoses of nervous brain cells usually cannot be found. The brain must control all the organs, tissues,

and their functions as fully in early infancy as at the later ages. Therefore it must contain all the cell centres and nervous fibres from early infancy.

There is no such necessity for any of the other organs, and it is sufficient if the number of the cells increases with the growth of the whole organism. Therefore, relative hypoplasia of the brain, which is larger than in other organs (except the spleen), is due not only to the effects of aging but also to the fact that at an early age the brain is more fully developed than the other organs.

Effects of Hormones.—No histologic investigation was carried out. From tables 2 to 4 it is possible to conclude that the brain weight, in contrast to most other organs, remains remarkably constant in spite of the various hormonal treatments used and variation in the weight of the senescent rats.

Hypophysis

Features of Aging.—In the present experiments histologic examination of the hypophysis was not made. Wolfe, Bryan, and Wright (62) found that in old female rats the weights of the hypophysis varied from 10 to 45 mg., in most cases being less than 17 mg. Abnormal cells were present in about 58 per cent of the rats: chromophobes and in some cases eosinphiles were enlarged, with large nuclei and nucleoli but containing little chromatin. In two hypophyseal adenomas described by these authors the cells were similar to those in the hypophyses of old rats. In our present experiments it was also found that the weight of the hypophysis varied from 11.2 to 22.6 mg. and, because of this variation, hypoplasia of this gland although present (table 1) was statistically not significant ($P > 0.05$).

Perhaps the occurrence of large pituitaries in some of the old rats has some connection with spontaneous development of adenomas (62) or carcinoma-like tumours (13, 49) in senescent or senile rats. Korenchevsky and Hall (31) observed similar hypophyseal tumours in old rats injected with dehydroandrosterone and testosterone propionate.

The histologic structure of adenocarcinomas is characterised by abundant mitoses, occurrence of giant cells and nuclei, and variation in the chromatin content of the nuclei, and differs from oestrogenic hypophyseal tumours, which are hyperplasias of the chromophobes.

Henderson and Rowlands (20) assayed the potency of 100 human pituitaries from persons of different ages. They found, in women during the menopause and in men 60 to 70 years old, a sudden rise of gonadotropins consisting almost entirely of follicle stimulating hormone. In spite of this rise of gonadotropins the output of sex hormones in old women falls drastically (8, 55, 63). In senile rats (41a) the pituitaries also contained more gonadotropins than did those of the adult animals. This was explained by the fact that in adult individuals gonadotropins are released from the hypophysis as rapidly as they are formed, while in the senile hypophysis they are stored for a longer time.

Effects of Hormones.—Effects of sex hormones on histologic structure of the hypophysis have previously been studied by several authors. They were well reviewed and summarised by Burrows (5). The results obtained indicated that oestrogens degranulate the basophils and eosinophils and increase the number of chromophobes. Oestrogens increase the size and weight of the hypophysis causing with larger doses development of adenomas in this gland.

Androgens also degranulate the basophils. While in some experiments the number and granulation of the eosinophils were not changed, in others an increase of eosinophils was recorded after administration of androgens. Effects of progesterone on the hypophysis cytologically were not studied sufficiently.

Oestrogens, androgens, and also progesterone depress the gonadotropic function of the anterior hypophysis. This is especially noteworthy in the case of oestrogens which, however, produce a simultaneous enlargement of

the gland, showing that enlargement of the hypophysis (as was also stated previously in the case of the thyroid gland) does not mean necessarily an increase in its function.

In the present experiments the only statistically significant change in weight of the hypophysis ($P < 0.02$-0.01) was a decrease of the gland (tables 2-4) after treatments with androgens in both experiments and after administration of all four hormones in experiment II. Small doses of oestradiol did not affect the weight of the hypophysis.

Preputial Glands

The effect of aging on the weight of the preputial glands was not noticeable (table 1). Significant enlargement of these glands in senescent females occurred (tables 2-4) after administration of androgens alone or in combination with other hormones.

Discussion

As in previous papers, it should be emphasised again that for a proper definition and complete ascertaining of the processes of aging and of the anti-aging properties of any factor examined, several morphologic, physiologic and biochemical investigations, both experimental and clinical, are necessary.

Therefore, most of the statements and conclusions arrived at in this paper must be considered as preliminary ones subject to confirmation by other manifold experiments and observations.

Spontaneous Features of Aging in Female Rats

1. *Dependence on the Strain of Rats.* It is well known that different strains of rats differ considerably in their growth and susceptibility to some infections. Thus in some strains the males might reach the weight of 750 gm. while in others the maximum weight would seldom be as much as 450 to 500 gm. Some are susceptible to chronic rat pneumonia, of which they usually all die before reaching the age of 2 years. Other strains are comparatively resistant to pneumonia but are more susceptible to chronic paratyphoid.

According to differences in the strains, features of aging in various strains might also be different. This is well known in the case of mice, if susceptibility to the development of carcinoma is taken as a feature of aging.

Therefore, some of the features of aging which in the present experiments were tentatively considered as such, might occur only in our strain of rats.

2. *Epithelial Meta-Hyperplasias.* For example, we recorded as a possible feature of aging epithelial meta-hyperplasias observed in the uterus, liver, pancreas, and thyroid of our untreated senescent rats. Obviously this feature is an important one, since in some of the treated rats these changes, with a gradual transition of normal into pathologic cells, were developing into adenoma-like structures or, as in the thyroid and parathyroids, apparently into true adenomas.

Therefore these meta-hyperplasias in the intact untreated rats might be considered as a preliminary stage from which in suitable conditions (hormonal overstimulation and senescence) adenomas might develop.

These changes, however, s h o u l d be defined as a conditional feature of aging since they might occur only in certain strains of rats just as carcinomas develop easily only in certain strains of mice.

These hyperplasias should also be included in a group of secondary features of aging since most probably they are produced not by basic but by some secondary causes of aging as defined previously (25).

It is necessary to emphasise that the epithelial hyperplasias in the untreated senescent rats (just like the round cell infiltrations discussed in the following paragraph) were minute in size, even when microscopically observed, and did not occur in every section of the affected organ.

3. *Round Cell Infiltrations.* Out of two available strains of rats, pneumonia susceptible and paratyphoid susceptible, the latter was

deliberately chosen for our experiments on senescent rats. This decision was prompted by the fact that so far there is no possibility of preventing rat pneumonia while a suitable vaccination might immunise against paratyphoid. Our strain of rats was obtained from the Breeding Farm Laboratories, scientifically controlled by a specialist, and in which paratyphoid epidemics had not been observed. In spite of this, all our rats were always vaccinated by a special Salmonella vaccine. At the dissection of our old or senescent rats no microscopic features of paratyphoid were recorded. This however, does not mean that some other chronic latent infection could not have occurred in our rats, for example, one caused by some other type of paratyphoid bacteria against which the vaccine used was ineffective.

Moreover although rarer and smaller than in the senescent rats, in a few young rats these round cell infiltrations were observed in the liver and kidneys but not in other organs. Therefore, more pronounced development of these round cell infiltrations might be produced by an aging accumulation of and autointoxication by some normal metabolic products or some abnormal products which are formed in senescent or senile organisms only. They might, however, be caused by some chronic infection which we failed to ascertain.

It is a great handicap to experimental gerontologic research on rats and mice that so far the standard strains of these animals guaranteed to be free of any infection are not available in any country.

4. *Apparently More Typical Features of Aging.* Into this group might be included relative hypoplasia of some organs, decrease or absence of mitoses, abnormal development of fibrous tissue (uterine mucosa, thyroid, parathyroids), some histologic signs of decreasing function in some organs (ovaries, thyroid), and decrease in number of giant cells in the spleen.

Most of the features of aging were present only in part of our rats. Most probably this should be explained by the fact that our rats were senescent (22 to 27 months old) and not senile animals (36 months or over). In our experience, in rats (as in human beings) the appearance of senescence and the rate of aging vary greatly.

Effects of Hormones

1. *Reversibility of Some Features of Aging.* —After treatment with the hormones used, especially in certain combinations, some features of aging were reversed towards or to the level observed at a younger age: thus, in certain organs the relative hypoplasia was reversed, multiplication of cells (as judged by the number of mitoses) was increased, some histologic signs of increased functions were observed (e. g., in the thyroid gland), and exterior appearance improved.

It is necessary, however, to emphasise that in our experiments only these few features and not all the processes of aging, i. e., senescence as a whole, were reversed. Moreover, it was not ascertained whether the reversals obtained might be maintained for a prolonged period.

The condition becomes still more complicated since, besides the apparently favourable results of hormonal treatments of senescent rats, some definitely harmful effects were obtained: hypoplasia of the ovaries, adrenals, and uterus, cystic hyperplasia of uterine glands, depressed function of the thyroid, myocardial lesions, tendency to development of adenoma-like structures in the liver, thyroid, parathyroids, adrenals, thymus, and pancreas, and sclerotic changes in the thyroid and parathyroids. These harmful effects occurred singly or in a group of two or more, some of them appearing after administration of one hormone only, some after treatment with a certain combination of the hormones.

Some harmful effects occurred in only a few of the treated rats, and at the same time, although in a weaker form, were also observed in the control untreated animals (e. g., sclerosis of parathyroids). In such cases their development into a pronounced pathologic process might mean simply that they were caused by some nonhormonal, senescence-producing fac-

tor and that the hormones were unable to stop the development of, or cure, these abnormal changes.

All these limitations and harmful effects, under no circumstances, should overshadow the most important conclusion that at least some processes of aging seem to be reversible.

This conclusion becomes especially significant since it was arrived at with methods which could probably be considerably improved by the inclusion of hormones of the anterior hypophysis and adrenal cortex into the plurihormonal treatment used in the present experiments; and in the case of some hormones, by decreasing the dosage, which seems to be too large for the rats. Thus, this gives some hope that the number of reversible processes of aging might be increased in the future when more complete methods and more effective factors, namely those relating to the basic causes of aging, will be discovered and used for the prevention and even the treatment of premature and pathologic senility.

2. *Nature of Adenoma-Like Structures.*—Ingrowth of these structures into neighbouring host-tissue was observed only in the thyroid, in a few cases in the thymus, and perhaps to a slight degree in the liver. This ingrowth, however, did not result in the formation of tumours breaking through and growing outside the thyroid or thymus. Metastases and giant cells were absent, and mitoses, except in some pancreatic adenoma-like structures, were comparatively few.

In the adrenals, pancreas, and liver, in spite of transitional cellular forms, these structures were well demarcated from the neighbouring tissues although (as was the case in the thyroid and pancreas) they were not covered by a capsule. Therefore the formations produced seem to belong to the group of benign adenoma-like structures.

They, however, contribute to the problem of the tumourogenic action of hormones. The adenoma-like structures, previously obtained (32) in the uterus of ovariectomised rats after simultaneous administration of testosterone propionate with oestradiol dipropionate or benzoate-butyrate, have a bearing on the same problem. The tumourogenic action of oestrogens in certain animals has been definitely established (19). There are also somewhat similar data for testosterone compounds (41).

3. *Antitumourogenic Action of Progesterone.*—Previously (30, 32, 37) metaplasia of the uterine epithelium of rats produced by oestrogens and the development of adenoma-like formations in the uterine mucosa caused by the administration of oestradiol compounds with testosterone propionate were described. In both cases the simultaneous administration of progesterone prevented the occurrence of the metaplasias and adenoma-like formations.

Lipschutz recorded and repeatedly confirmed that in guinea pigs by administration of oestrogens it is possible to produce fibromata of the uterus as well as anywhere on serous membranes of the abdominal cavity. He found (42) that the best antifibromatogenic compound preventing the formation of these tumours is progesterone. These properties, to a lesser degree, were also found by Lipschutz in some other steroids: desoxycorticosterone acetate, dehydrocorticosterone, testosterone, and testosterone propionate.

In contrast to these important results, it is necessary to emphasise that, in the previous experiments on rats (32), the combination of oestradiol with testosterone propionate originated uterine adenoma-like structures, and that, in the present experiments on senescent rats, adenomas of the thyroid, and parathyroid, and adenoma-like structures of the liver, adrenals, thymus, and pancreas occurred in the rats, to which were administered testosterone propionate alone or progesterone with oestradiol or other hormones simultaneously.

Lacassagne (40) also failed to modify the appearance in mice of mammary adenocarcinoma caused by oestrogens by administration of progesterone or testosterone.

This indicates that progesterone and testosterone cannot be considered as general antitumourogenic agents but that they are effective

only against certain types of metaplasias and tumours.

Summary

1. Investigation in the weights of organs and fat deposition and histologic examination were made in 121 normal senescent female rats, aged 22 to 27 months, in order to study the effects of progesterone and oestrogenic, androgenic, and thyroid hormones on certain processes of senescence. In addition, in order to study the natural relative hypoplasia of organs in senescence, the 17 control rats were pooled with 10 other untreated senescent rats of about the same age and compared with 14 young rats about 7 to 8 weeks old.

2. In agreement with similar results from our previous experiments on the aging hypoplasia in adult female rats (and also in male rats and human beings), the relative hypoplasia of some organs was observed in senescent female rats as well. This change, which occurred in nearly all rats with aging, might be considered as one of the specific features of aging, as might also a decrease in number, or absence, of mitoses.

3. Some pathologic changes, mostly slight in degree, were found in some of the organs of untreated female senescent rats and were tentatively suggested as also being features of aging (subject to confirmation on a larger number of animals)—namely, sclerotic development of fibrous tissue, epithelial hyperplasias, decrease in number of giant cells in the spleen, histologic signs of decreased functions, and, perhaps, more pronounced minute round cell infiltrations. At present these changes might be considered as conditional features of aging since most of them occurred only in part of the animals, or they might be present in some strains of rats only.

4. In senescent rats the effects of hormones administered singly or in combinations were similar to, but in certain ways weaker than, those previously obtained in adult rats with artificial climacteric.

5. The hormones investigated possessed two opposite, more or less pronounced, properties producing simultaneously an apparently favourable action, namely, hypertrophy or stimulation of some organs and depressing or other harmful pathologic effects.

6. Because of its apparently favourable action, the hormonal, especially plurihormonal, treatment stopped aging involution of some organs in senescent rats and, moreover, even reversed the relative weight of these organs, and apparently certain histologic features as well, towards or to the level observed at a younger age.

7. Therefore, in the experiments performed at least some processes of aging seem to be reversible and can be influenced arbitrarily.

8. This fact should not be overshadowed by the simultaneous occurrence of depressing or other pathologic changes observed in some organs of some of the treated rats.

9. These harmful changes might indicate that the treatment was deficient, most probably in various ways, as, for example, in the correct dosage and absence in the combinations used of such important hormones as those of the anterior hypophysis and adrenal cortex.

10. In all experiments, however, which deliberately or as in our investigation accidentally are of an anti-aging nature, the most important deficiency is the impossibility of including the operation of the factors affecting the basic causes of aging.

11. One or more of the following harmful effects were observed in some senescent rats after hormonal treatment: hypoplasia of the ovaries, adrenals, and uterus, cystic hyperplasia of the uterine glands, depressed function of the thyroid, myocardial lesions, and development of adenoma-like structures in the liver, adrenals, thyroid, parathyroids, thymus, and pancreas.

12. Development of these changes elucidated and emphasised the hormonal aetiology of these pathologic lesions in the cases of hyperfunction or dysfunction of the respective endocrine glands.

13. As in previous experiments on ovariectomised rats, in the senescent rats simultaneous administration of the hormones prevented,

partly or completely, some damaging effects due to hyperhormonization produced by a single hormone (in the case of uterus, ovaries, adrenals, and thyroid).

14. In gerontologic research especially responsible are all attempts to reverse the organism, its organs and functions, to the level observed at a young age. Many prolonged and many-sided (morphologic, physiologic, biochemical, etc.), investigations are necessary in order to ascertain the true value and harmlessness of any apparently anti-aging factor. The results obtained in the present experiments emphasise this strongly and warn against hasty application of experimental results for therapeutic treatment.

15. Rejuvenation of the aging organism is very far from being the only way of bringing about normal aging and a normal old age. A rapid approach towards normal old age can be achieved by the elimination and prevention of all those diseases which complicate the present day abnormal senility but which are not the features of normal aging. A still nearer approach towards the ideal standard of old age biologically possible for the species will be made by the elimination of those secondary and primary causes of aging which could be influenced arbitrarily.

TABLE 1. EFFECTS OF AGING ON RELATIVE WEIGHTS OF ABDOMINAL FAT AND ORGANS PER 200 GM. OF FAT-FREE BODY WEIGHT IN 27 SENESCENT NORMAL UNTREATED FEMALE RATS AS COMPARED WITH 14 YOUNG RATS.

	Young Rats†	Senescent Rats
Body Weight (actual, Gm.)	92.0	241.0
Abdominal fat (Gm.)	1.7	21.8
Ovaries (mg.)	77.6	52.1
Uterus (mg.)	465.0	657.0
Vagina (mg.)	470.0	424.0
Preputial glands (mg.)	101.0	95.0
Adrenals (mg.)	73.5	62.1
Thyroid (mg.)	27.8	20.0
Hypophysis (mg.)	18.4	16.9
Thymus (mg.)	576.0	81.0
Liver (Gm.)	10.43	7.57
Kidneys (Gm.)	1.96	1.62
Spleen (mg.)	1634.0	685.0
Heart (mg.)	1009.0	843.0
Brain (Gm.)	4.01	2.23

† Since ovaries, uterus, adrenals, and hypophysis usually reach highest weight at sexual maturity, these data were taken from rats 118 days old; the remaining data from rats 49–56 days.

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TABLE 2. EXPERIMENT I. EFFECT OF PROGESTERONE, OESTRADIOL B. B., ANDROGENIC AND THYROID HORMONES ON ACTUAL WEIGHT OF ABDOMINAL FAT AND ORGANS IN SENESCENT NORMAL RATS.

Weekly doses: progesterone in crystals 10 mg.; androsterone benzoate in crystals 5–75 mg.; testosterone propionate in crystals 2–4 mg.; desiccated thyroid 85 mg. twice a week; oestradiol B. B. 0.015 mg. 3 times during first 10 days only.

Organs	Controls	Oestradiol B. B.	Thyroid Desiccated	Progesterone + Oestradiol B. B.			Testosterone Propionate	
				Alone	+ Thyroid Desiccated	+ Thyroid Desiccated + Androsterone	Alone	+ Oestradiol B. B. + Thyroid Desiccated + Progesterone
Ovaries (mg.)	48	45	63	34	32	29	24	22
Uterus (mg.)	622	693	638	711	697	651	844	959
Vagina (mg.)	367	414	435	452	498	479	598	587
Preputial glands (mg.)	93	65	143	115	126	144	272	214
Adrenals (mg.)	57	58	62	61	73	69	43	60
Thyroid (mg.)	16.3	18.0	17.2	20.3	20.7	17.8	19.9	17.9
Hypophysis (mg.)	15.5	17.4	13.9	14.6	14.8	15.2	12.2	14.8
Thymus (mg.)	60	70	64	50	66	57	39	42
Liver (Gm.)	7.13	7.29	6.87	7.68	8.54	8.18	6.96	7.62
Kidneys (Gm.)	1.48	1.61	1.75	1.53	1.96	1.80	1.74	1.84
Spleen (mg.)	694	622	856	724	977	905	665	972
Heart (mg.)	766	844	921	889	998	981	880	931
Brain (Gm.)	1.98	2.00	2.00	1.99	2.05	2.00	2.04	2.02
Abdominal fat (Gm.)	21.7	18.5	11.4	28.6	14.1	15.5	13.4	9.7
Final body weight (Gm.)	245	246	220	277	252	241	234	233
Gain (+) or loss (−) in body weight (Gm.)	+8	+10	−16	+36	−2	−3	0	+4
Number of rats in each group	9	6	7	8	6	9	9	8

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TABLE 3. EXPERIMENT II. EFFECT OF PROGESTERONE, OESTRADIOL B. B., ANDROGENIC AND THYROID HORMONES ON ACTUAL WEIGHT OF ABDOMINAL FAT AND ORGANS IN SENESCENT NORMAL RATS.

Doses: androsterone and progesterone in crystals 10 mg. each, once in 10 days; desiccated thyroid 60 mg., 3 times a week; oestradiol B. B. 0.015 mg. twice, during first week only; testosterone propionate-pellet 20 mg.

Organs	Controls	Androsterone	Testosterone Propionate	Thyroid Desiccated	Oestradiol B. B.				
					Alone	+ Thyroid Desiccated	+ Progesterone	+ Progesterone + Thyroid Desiccated	
								+ Androsterone	+ Testosterone Propionate
Ovaries (mg.)	45	27	31	65	47	57	45	27	24
Uterus (mg.)	765	301	920	525	750	898	537	500	1339
Vagina (mg.)	391	382	603	417	443	433	426	453	575
Preputial glands (mg.)	84	232	267	122	88	108	95	257	292
Adrenals (mg.)	54	39	47	62	56	63	58	52	60
Thyroid (mg.)	21.6	22.0	20.1	19.4	20.2	18.3	21.4	23.0	21.3
Hypophysis (mg.)	15.1	12.5	12.5	15.8	16.4	17.2	14.4	12.8	13.8
Thymus (mg.)	71	66	43	85	85	79	65	72	50
Liver (Gm.)	6.93	7.46	7.87	7.40	6.81	8.30	7.87	9.22	8.23
Kidneys (Gm.)	1.57	1.64	1.78	1.74	1.39	1.81	1.59	2.10	1.96
Spleen (mg.)	648	672	588	705	610	792	755	1044	914
Heart (mg.)	769	916	929	908	815	922	882	1024	1013
Brain (Gm.)	1.99	1.99	2.03	2.07	2.08	2.05	2.01	2.08	2.11
Abdominal fat (Gm.)	23.8	30.3	21.1	20.8	28.1	18.1	29.7	22.6	15.2
Final body weight (Gm.)	256	280	264	243	260	246	287	269	254
Gain (+) or loss (−) in body weight (Gm.)	+10	+39	+21	−6	+17	0	+30	+20	+5
Number of rats in each group	8	6	7	5	5	6	7	7	8

TABLE 4. EXPERIMENT II. EFFECT OF PROGESTERONE, OESTRADIOL B. B., ANDROGENIC AND THYROID HORMONES ON RELATIVE WEIGHT OF ABDOMINAL FAT AND ORGANS PER 200 GM. OF FAT-FREE BODY WEIGHT IN SENESCENT NORMAL RATS.

Organs	Controls	Androsterone	Testosterone Propionate	Thyroid Desiccated	Oestradiol B. B.			Oestradiol B. B. + Progesterone + Thyroid Desiccated	
					Alone	+ Thyroid Desiccated	+ Progesterone	+ Androsterone	+ Testosterone Propionate
Ovaries (mg.)	49	29	32	72	55	60	47	27	23
Uterus (mg.)	851	329	926	605	883	944	562	506	1178
Vagina (mg.)	435	417	612	480	519	459	447	456	560
Preputial glands (mg.)	92	254	275	140	103	114	98	257	287
Adrenals (mg.)	61	43	48	71	65	66	61	52	58
Thyroid (mg.)	24.3	24.0	20.5	22.2	23.6	19.4	22.1	23.2	20.8
Hypophysis (mg.)	18.0	13.8	12.7	17.8	19.1	18.0	15.0	12.8	13.1
Thymus (mg.)	81	73	43	96	100	84	65	73	49
Liver (Gm.)	7.67	8.16	8.00	8.39	7.92	8.77	8.20	9.32	7.98
Kidneys (Gm.)	1.74	1.80	1.81	1.97	1.61	1.92	1.65	2.12	1.89
Spleen (mg.)	715	738	602	800	718	835	785	917	883
Heart (mg.)	854	1004	944	1026	948	974	925	1028	982
Brain (Gm.)	2.22	2.19	2.06	2.36	2.43	2.17	2.10	2.10	2.06
Abdominal fat (Gm.)	26.9	33.6	22.0	24.3	32.5	19.2	31.8	22.7	15.2
Number of rats in each group	8	6	7	5	5	6	7	7	8

TABLE 5. EFFECTS OF HORMONES ON ADRENAL ZONES AND CELLS IN EXPERIMENT II AND ON OCCURRENCE OF DEGENERATION IN GLOMERULOSA AND FASCICULATA ZONES IN EXPERIMENTS I AND II.

Groups	Area of Tranverse Section					Average Diameter of Fasciculata Cells	Percentage of Adrenals with Degeneration
	Cortex	Z. Glomerulosa	Z. Fasciculata	Z. Reticularis	Medulla		
Controls	189	17	120	52	41	4.7	59
Androsterone	140	16	78	46	44	3.8	57
Testosterone propionate	161	15	102	44	48	4.0	43
Thyroid desiccated	206	18	132	56	45	4.6	50
Oestradiol B. B.	179	17	118	44	43	4.8	64
Oestradiol B. B. + + thyroid desiccated	213	16	140	57	41	5.0	67
Oestradiol B. B. + + progesterone	192	19	118	55	44	4.4	50
Androsterone + + 3 other hormones	163	17	97	49	46	4.4	44
Testosterone propionate + 3 other hormones	188	15	109	64	38	4.5	25

Size of the zones and medulla in cross sections of the whole adrenal is expressed in sq. cm. as measured by planimeter at magnification 55. Size of the fasciculata cells in divisions of, and as measured by, ocular micrometer at magnification 311.

TABLE 6. EFFECTS OF HORMONES ON LIVER CELLS IN EXPERIMENT II AND ON MITOSES AND BILE DUCTS IN BOTH EXPERIMENTS.

Groups	Weight of Paper Replica of Average Cell (Mg.)	Percentage of Large Cells	Percentage of Large Nuclei	Number of Mitoses in Standard Area		Percentage of Livers with Bile Duct Hyperplasia (All Sizes)
				Experiment I	Experiment II	
Controls	7.44	13.5	2.8	5.7	9.8	18
Androsterone	8.46	23.9	8.1	—	5.3	33
Testosterone propionate	7.87	16.6	4.6	13.1	5.7	25
Thyroid desiccated	7.42	13.0	15.2	102.4	22.9	42
Oestradiol B. B.	7.94	19.0	5.1	14.0	10.7	27
Oestradiol B. B. + thyroid desiccated	7.41	15.5	13.8	—	13.1	50
Oestradiol B. B. + progesterone	7.50	19.0	6.8	11.6	6.0	27
Oestradiol B. B. + progesterone + thyroid desiccated	—	—	—	113.3	—	50
Androsterone + 3 other hormones	7.65	15.9	13.8	53.4	14.3	25
Testosterone propionate + 3 other hormones	7.59	14.2	8.7	35.2	10.2	38

TABLE 7. EFFECTS OF HORMONES ON KIDNEY TUBULES, NUMBER OF MITOSES, AND OCCURRENCE OF PATHOLOGIC CHANGES IN KIDNEYS.

	Weight of Paper Replica (Mg.) of Kidney Tubules		Number of Mitoses in Standard Area	Percentage of Kidneys with	
	Average Tubule	Average Lumen		Round Cell Infiltrations	Oedema of Glomeruli, and Casts
Controls	7.05	0.97	1.1	53	41
Androsterone	7.61	1.10	1.5	67	67
Testosterone propionate	8.21	1.19	3.0	13	19
Thyroid desiccated	7.99	1.01	1.8	50	58
Oestradiol B. B.	7.22	0.83	2.1	37	64
Oestradiol B. B. + thyroid desiccated	7.97	1.07	1.3	17	83
Oestradiol B. B. + progesterone	7.17	1.08	1.5	38	31
Oestradiol B. B. + progesterone + thyroid desiccated	—	—	—	17	50
Androsterone + 3 other hormones	7.83	1.25	2.9	31	50
Testosterone propionate + 3 other hormones	8.93	1.19	2.4	44	31

In the first three columns the data were taken from experiment II; in the last two columns experiments I and II were pooled.

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Problems of Sampling and Interviewing in Studies of Old People

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DR. HAVIGHURST OUTLINES THE METHOD USED IN ASCERTAINING THE NUMBER OF PEOPLE OVER 65 YEARS OF AGE IN A STUDY OF A TYPICAL MIDWESTERN COMMUNITY AND REPORTS THAT APPROXIMATELY 75 PER CENT OF THIS AGE GROUP COULD BE REACHED BY PERSONAL CONTACT, THE BALANCE BEING EITHER TOO ILL OR REFUSING.

THE adjustment of older people is just now being explored as a field for research. In this new field there lie problems of sampling and of interviewing that do not appear with studies of other age groups. The principal previous studies have been made with children, who are much more accessible than adults to research, since they are all together in school, their names and ages can easily be secured, and they are readily brought to cooperate in a research study. Old people, on the other hand, must be sought out individually, many of them are in such poor health that they cannot easily be interviewed, and they have adult defenses against research procedures which children accept and usually enjoy.

In this paper the typical problems of sampling and interviewing in studies of older people will be described and analyzed. These are problems which I encountered in the course of studies made by questionnaire and by interview with several groups of older people of various socio-economic statuses. They appear most clearly in a community study including all the people over 65 in a small midwestern city which is being made (5). Consequently this study will be described briefly as a background for presenting problems of sampling and interviewing.

The purposes of the study are: to describe the social and personal characteristics of the older people of a typical midwestern town, and, to discover the adjustment problems of these older people and to see how these problems are related to sex, age, social status, and marital status.

The community is a county-seat town in a midwestern state, with a 1940 population of 6100. It was selected for study because it is typical, on a number of census characteristics, of the cities between 5000 and 10,000 in population in the twelve north central states. There are 108 such cities which are the largest population centers in counties that are agricultural-industrial. This type of county has between 25 and 50 per cent of its gainfully employed males in agriculture, and the remainder in industry, business, and other occupations.

The community chosen for study, which shall be called Prairie City, is relatively complete and self-sufficient. Lying outside a metropolitan area, it has an independent social life; there is no college, university, or state institution in the community, nor is it a health or summer resort. Its local coherence and autonomy are therefore undisturbed (7).

According to the 1940 census, 10 per cent of the population of this community were aged 65 or over. This compared with 6.8 per cent for the United States as a whole and 7.1 per cent for the state in which Prairie City is located. There are 21 towns of the same type as Prairie City in the state, and their proportions of persons 65 and over range from 7.3 per cent to 13.3 per cent, with Prairie City almost exactly at the mean and the median of these cities.

THE TOTAL GROUP TO BE SAMPLED

As a basis for a satisfactory sampling procedure it is desirable to have a list of all the people in the group to be sampled—in this case, all the people aged 65 and over in the community during 1948. Such a list is extremely

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Since 1941 he has been at the University of Chicago, first as Secretary and later as Chairman of the Committee on Human Development. He has written a number of papers and books on the social psychology of child development. From 1944 to 1948 he was Chairman of the Committee on Social Adjustment in Old Age of the Social Science Research Council. He is co-author of *Personal Adjustment in Old Age,* and is a member of the Committee on Later Maturity of the University of Chicago.

difficult to obtain in American cities, where no central register of names and ages is maintained. However, the sugar rationing registration of May, 1942, secured a fairly complete registration, with age given in most instances on the registration cards. The sugar rationing registration became the basis for the list of names in the study.

Thus the names of all people who registered for sugar rationing in 1942 and who would be 65 or over in 1948 were listed. This list had to be corrected to eliminate those who had died or moved away between 1942 and 1948 and to add the names of those who moved into the community after 1942 and those who did not register for sugar rationing. New names were secured principally from three sources: the Old Age Assistance list, church membership lists, and the list of those living in two convalescent homes for older people. Names of those who had died or moved away since 1942 were identified through interviews with several informants, including city officials, clergymen, and several elderly people with wide acquaintance in the community.

In these ways a list of approximately 670 names was secured. This compared with 610 people 65 and over according to the 1940 census. The number in 1948 was probably close to 670, since the proportion of older people is generally increasing. The community of Prairie City did not grow much between 1940 and 1948 but may have added two or three hundred to its total population. The list of 670 names included a few individuals whose ages were estimated too high, as well as some who had died, and failed to include other individuals who were actually 65 or over. (A check on one-third of these names showed that 6 per cent of the names referred to people who were too young or who had died.) Probably 95 per cent of the people over 65 were on the list. From Prairie County there were nine people over 65 in the state hospitals for the insane, and one person over 65 in a state colony for the feeble-minded. Since Prairie City has about one-third the population of Prairie County, only three or four names would probably be added to the list of old people in Prairie City if these people were included.

There is no reason to suppose that there were any systematic omissions of groups of people from the list, except that there was probably an omission of a few people just past 65 who had moved into the community since 1942 and whose appearance was middle-aged rather than older. Because there were no rationing registrations available for these people, they were identified only by informants who had to estimate their ages.

Since it was desired to sample the old age population principally according to the categories of sex, socio-economic status, and marital status, these data had to be secured for all the people on the list. Marital status was obtained from the city directory in the case of people who were married and living with their spouse. Other types of marital status were determined through interviews with people who had a wide acquaintance in the com-

munity. All told, approximately a hundred interviews were made in order to obtain the necessary information on marital status, age, occupation, and other characteristics.

Socio-economic status was determined with the use of Warner's Index of Status Characteristics (8). For this index it is necessary to have data on house type, ecologic area, source of income, and occupation (or former occupation if retired, husband's former occupation if a widow). House type and ecologic area had already been determined for all houses in the city, and consequently the person's address was sufficient for these two items. Addresses were secured from the city directory and from precinct voters lists. Occupation was given for many men in the city directory, and principal source of income could be inferred in most cases from knowledge of a person's occupation. Interviews with widely acquainted informants were necessary in order to obtain occupational data for retired men and for deceased husbands of widows.

The question of accuracy of age data was raised early in the study. Did old people report their ages accurately on the sugar rationing registration? A partial answer to this question could be obtained in the cases of 38 people who had ages recorded on sugar rationing cards and who were receiving Old Age Assistance in 1948. Since birth-date must be verified before a person can receive Old Age Assistance, it was assumed that the OAA records were accurate.

When age as given on the rationing registration was compared with age on the OAA record, it was found that there was no discrepancy in 33 cases, 2 men reported themselves older on rationing registration, and 3 women reported themselves younger on rationing registration. These errors were small and could at the most result in omission of a few women from the list who had recently passed 65. A greater source of error in the age data lay in the estimates which were made by informants in cases where there were no age data from sugar rationing. This source of error was evaluated later in the course of the field work and will be discussed further.

Table 1 shows the distribution of the older people in Prairie City by sex, age group, socio-economic status, and marital status. The table

TABLE 1. DISTRIBUTION PER THOUSAND OF PEOPLE 65 AND OVER IN PRAIRIE CITY, BY AGE GROUP, SEX, SOCIAL CLASS, AND MARITAL STATUS IN 1948.

Age	Social Class	A Upper		B Upper-Middle		C Lower-Middle		D Upper-Lower		E Lower-Lower		Total		
	Marital Status	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Both Sexes
65-74	Married	6	8	27	22	66	54	78	51	36	12	214	147	361
	Widowed		3	5	20	13	54	23	69	6	13	47	160	207
	Single	—	—	2	2	11	11	11	9	13	0	36	21	57
	Divorced	—	—	—	—	2	—	2	2	3	—	6	2	8
	Total	6	10	33	44	92	119	115	131	59	25	303	330	633
75+	Married	2	—	18	9	18	3	20	11	2	3	59	26	85
	Widowed	2	11	5	33	9	59	26	62	9	17	50	180	230
	Single	—	—	2	2	5	11	13	5	6	2	26	18	44
	Divorced	—	—	—	—	1	—	2	2	3	—	6	2	8
	Total	3	11	24	44	33	72	60	78	20	21	141	226	367
	Grand Total	9	21	57	87	125	191	175	209	78	47	444	556	1000

Totals of rows and columns will not always correspond exactly to the numbers in rows and columns, because decimals have been rounded off.

is based on 664 cases, but the numbers have been transformed to a basis of one thousand. Assuming one thousand people aged 65 and over, they would be distributed in the way shown in table 1. The socio-economic groups A, B, C, D, E, in table 1 correspond to the social classes designated by Warner as upper, upper-middle, lower-middle, upper-lower, and lower-lower, respectively (8).

Drawing the Samples

Two samples were drawn from the total group. One, called the ABQ sample, is a stratified sample drawn so as to secure large enough numbers of the smaller groups to permit statistical work with them. In drawing this sample, cards were made out for all persons over 65, and these cards were then divided on the basis of sex. Then followed a subdivision into five social classes. Each class was further divided as to marital status, and each marital status group was divided as to religion (Catholic or non-Catholic), and as to ethnicity (native-born, Norse, or Polish). This resulted in a large number of categories of which approximately 100 included entries. There were other possible categories (*e.g.*, upper class of Polish birth) which were empty of names.

Cards were then drawn at random from each category group so as to provide a minimum of about 15 persons in each marital status, religious group, ethnic group, and social class. A particular name might appear several times, once in a marital status group, once in a religious group, and so on. Thus a stratified sample was obtained, which included as many as half of the smaller groups (*e.g.*, upper class persons, single persons, Norse and Polish-born, and Catholics). In the more populous categories the number taken was roughly one out of six. The total number in the ABQ sample is 137.

Originally there were two stratified samples: the A and the B samples, each containing about 100 names. The B sample was designed to serve as a supplement to the A sample. Individuals were drawn from the B sample to fill in the gaps in the A sample caused by errors in the data on age and socio-economic status, by illness, and by refusals. Then a few further names were drawn from the total list to fill up certain categories of the Q-sample, as will be explained below. Some of the people in the original B sample were not interviewed.

The second sample, called the Q-sample, is a group of 100 people drawn to represent the entire old age population of Prairie City by age, sex, socio-economic status, and marital status. The numbers of people in each of these categories were determined so as to make the Q-sample correspond as closely as possible to the distribution shown in table 1. The Q-sample was drawn as follows: when the AB group contained more persons of a given category than were needed in the Q-sample, such as the upper social class, the desired number of cases was drawn at random from the cases in the AB group; when the AB group did not contain enough persons of a given category to supply the Q-sample fully, as in the case of lower-middle class married women, all the cases of that category in the AB group were taken and enough more cases were drawn at random from the total group to fill out the required number.

Table 2 shows the composition of the Q-sample. It represents the total old age group quite well except in the following respects. There is no divorced person in the Q-sample because there were too few such persons in any particular age and social class group to make up 1 per cent of the total age group. There is a slightly larger proportion of Catholics in the Q-sample than in the total age group (29 per cent compared with 20 per cent). There are slightly larger proportions of Norse-born people and of Polish-born people in the Q-sample than in the total age group (12 per cent of Norse compared with 9 per cent in the total age group and 6 per cent of Polish compared with 4 per cent in the total age group). These departures from an ideal sampling pattern are due to the fact that the AB (stratified) sample was drawn to contain relatively large proportions of minority groups, such as Catholics and foreign-born, and conse-

TABLE 2. THE Q SAMPLE. TOTAL N = 100.

Social Class		Upper		Upper-Middle		Lower-Middle		Upper-Lower		Lower-Lower		Total		
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Both Sexes
Marital Status	Married	1	1	5	3	8	6	10	6	4	1	28	17	45
	Widowed	—	1	1	5	2	11	5	13	2	3	10	33	43
	Single	—	—	—	1	2	2	3	1	2	1	8	4	12
Religion	Protestant or Nominally Protestant	1	1	5	7	11	13	10	14	6	3	33	38	71
	Catholic	—	1	1	2	1	6	8	6	2	2	12	17	29
Ethnic Group	Native American	1	2	6	9	9	15	12	15	6	4	34	45	79
	Norse	—	—	—	—	3	4	2	1	1	1	6	6	12
	Polish	—	—	—	—	—	—	2	3	1	—	3	3	6
	Other Foreign Born	—	—	—	—	—	—	2	1	—	—	2	1	3
Age	65-74	1	1	3	5	8	12	12	13	6	3	30	34	64
	75+	—	1	3	4	4	7	6	7	2	2	15	21	36
	Total	1	2	6	9	12	19	18	20	8	5	45	55	100

quently these same groups were overrepresented in the Q-sample when it was drawn from the AB sample.

PROBLEMS OF INTERVIEWING

In order to secure information from as many people in the samples as possible, and to secure as much good information as possible from these people, the interview method was used in preference to a mailed questionnaire. Most of the interviewing was done by a young woman over a period of nine months, but a young man also worked in the field for three months, interviewing mainly men. The interviewers tried a number of approaches, including letters, telephone calls for appointments, and simple door-bell ringing. Telephone calls for appointments were made with most of the middle class and upper class people. With the lower class people and with people in the middle classes who seemed difficult to approach, house calls were generally used without preliminaries. A few men were located and interviewed in the taverns where they habitually spent a great deal of time.

The interviewer usually started by identifying herself as from the University of Chicago and saying that she was interested in knowing how older people thought about things and how their experience could be used to help other people. The conversation was kept on the social call level until rapport was established, when a schedule was brought out and filled in, usually by the interviewer as the subject responded to the questions. Often the schedule was not used until a second call was made. The interview itself was designed to throw light on various aspects of the subject's experience—his family life, social activities, social participation, and his attitudes about aging.

Sometimes a subject could not be seen because he was ill or was out of the city. All such cases were followed up later and all of them were seen, unless they became too ill. There were also a number of refusals. When a person refused to talk with one of the field workers, the other field worker attempted a different approach, and in this way several initial refusals were converted into successful contacts.

The great majority of older people were cooperative and seemed to welcome the visits of the field workers. Many of these old people said that they were lonely and were glad to have visitors. The minority who were not interviewed fell into two general categories. One group could not be seen because they were too ill or too feeble. The interviewers could not themselves always certify that these people were too ill or too feeble; they had to take the word of the nurse or relative who was caring for the person in question. Among this group of the too ill and feeble were the several people who died during the field work before the interviewers reached them. A total of 9 per cent of the original ABQ group were too ill and feeble to be seen and another 4 per cent died before the field workers were able to see them. The interviewers did see a few people who were quite ill or feeble but were not so well protected and therefore were accessible to strangers.

The second principal category of those who were not interviewed was the refusals. These were people who simply refused to talk with the interviewer, or, in a few cases, whose spouses or children refused to let the interviewer see them. The refusals amounted to 11 per cent of the total ABQ group. While there were refusals in every social class, in both age groups, and in both sexes, there seem to have been two groups who were especially likely to refuse. These were upper class widows and lower-middle class women and men. Sixteen out of the total of 23 refusals came from these groups. The upper class women who refused were polite but firm. The lower-middle class people who refused tended to be suspicious and hostile. The social classes who were the easiest to interview were the upper-middle and lower-lower classes. There was only one refusal in each of these groups.

Interviewing people in the upper-middle class was relatively easy probably because such people tend to be interested in social problems and in civic welfare. Consequently they understood the purposes of the study and accepted it as a useful thing even though it would not help them personally. The other class which proved relatively easy to interview was the lower-lower. Many of these people are accustomed to visits from social agency representatives and accept an interview as a matter of course. In addition it is probably true that many of the lower class people are flattered by the attention they get from the interviewer and are glad to have such a break in a rather monotonous existence.

It is perhaps significant that the woman field worker received no refusals from men but she was refused by several women. The male field worker was refused by both men and women.

In order to give a general idea of the experience with interviewing, table 3 has been set up to show the results of field work with the original ABQ group of 234 persons. This number is a third of the old people in the community and is probably fairly representative of the total group. The table reports the results obtained from 208 of the 234 names on the ABQ list. The remaining 26 names represented people who were not interviewed because they were not needed for the AB or the Q samples. Nevertheless, these names were verified as to age and residence in the community.

Table 3 shows the following findings:

There were some errors in the data for the 234 people. Six per cent were either below 65, or had died before 1948, and consequently should not have been on the list. Socio-economic data were in error on 9 per cent of the cases. Marital status was in error in 3 per cent of the cases; almost always the error consisted of listing a person as married and living with spouse when he or she was widowed.

A small group (3 per cent) moved away from the community during the field work and thus were lost to the study.

A group of 9 per cent were too ill and feeble to be seen and 4 per cent died during the course of the field work before they were seen.

A group of 11 per cent refused to be interviewed.

TABLE 3. RESULTS OF FIELD WORK ON ORIGINAL ABQ GROUP.

Age	Social Class	Schedule Secured		Refused		Too Ill		Died 1948		Too Young		Died Before 1948		Moved Away		Not Needed for Sample		Correction in Social Class*†		Correction in Marital Status*		Totals		
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Both Sexes
65-74	A	3	4	–	3	–	–	1	–	–	–	–	–	–	1	–	–	–	–	–	–	4	8	12
	B	6	6	–	–	–	1	–	2	–	–	–	–	–	–	2	2	–	–	–	–	8	11	19
	C	10	10	4	4	–	2	–	–	–	2	–	–	–	3	2	2	2 –	4 –	–	1	16	23	39
	D	17	16	2	2	1	1	–	–	2	3	–	1	–	1	5	5	1 1	– –	–	–	27	29	56
	E	7	3	–	–	–	–	1	1	1	–	2	–	–	–	–	1	4 –	2 –	–	–	11	5	16
	Total	43	39	6	9	1	4	2	3	3	5	2	1	0	5	9	10	8	6	–	1	66	76	142
75+	A	2	2	–	–	–	5	–	–	–	–	–	–	–	–	–	–	–	–	–	1	2	7	9
	B	6	8	1	–	–	2	2	1	–	–	–	1	–	–	–	–	–	–	1	1	9	12	21
	C	4	11	1	4	1	3	–	–	–	–	–	1	–	1	2	2	–	–	–	–	8	22	30
	D	8	6	1	–	–	3	–	1	–	–	–	1	–	–	1	–	1 1	1 –	1	1	10	11	21
	E	6	2	1	–	–	–	–	–	–	–	–	–	–	–	2	–	– –	1 –	1	–	9	2	11
	Total	26	29	4	4	1	13	2	2	0	0	0	3	0	1	5	2	2	2	3	3	38	54	92
	Grand Total	69	68	10	13	2	17	4	5	3	5	2	4	0	6	14	12	10	8	3	4	104	130	234

* Numbers in these columns are included in preceding columns.

† Numbers in the upper half of the space indicate revision upward in status; numbers in the lower half of the space indicate revision downward.

Two-thirds of the group were interviewed. This figure should be revised upward because 6 per cent of the group were people who did not belong in the age group, an additional 3 per cent had moved away, and 4 per cent died before they were interviewed. Consequently, the interviewers' record of acceptances was 76 per cent of those who were actually in the age group and in the community at the time of the field work.

Since 76 per cent of the old-age group were interviewed, the inference can be made that the Q-sample represents not all the old people in the community but all except two significant groups: those who are too ill and feeble to be interviewed, and those who refused to be interviewed.

The loss to the study of those who were so ill and feeble that they could not be interviewed and those who died before the interviewers

visited them is not a serious loss. This group can be thought of as already on the periphery of life, not "visible," or they may be thought of as a special group, deserving special study. The present study does not represent them. Leaving this group out of consideration, the proportion who were interviewed rises to 87 per cent of the people who were in good enough health to be seen by interviewers.

It is the 13 per cent of the "visible" old age population who refused to be interviewed that arouse questions about the representative nature of the Q-sample. This sample may be said to represent 87 per cent of the old age population who are in good enough health to be seen by interviewers. The question which plagues the research worker is—in what respects do the 13 per cent of refusers differ from the 87 per cent of cooperators? This study is seeking to throw some light on the question by comparing the 13 per cent with the 87 per cent on some things which can be found out about them without their cooperation. For example, the refusers tend to cluster in the upper class and the lower-middle class. Hence the AB and Q samples may not represent these social classes as well as they represent the other classes.

Comparison With Other Studies

It is useful to compare the experience in sampling and interviewing of this study with analogous experience in other studies. Comparisons may be made with a number of recent studies (2, 3, 4, 6). In all of these studies a list of names of people over 65 was obtained and schedules were mailed to them, or they were interviewed. The lists probably had about the same order of validity as the ABQ list after the names of those under age and deceased have been taken off the latter. Results of work with these groups are as follows:

Present study.—Interviews were held and schedules filled out with 76 per cent of the group. Outright refusals were 13 per cent.

Study of retired YMCA secretaries.—Two schedules were mailed to members of the group with a covering letter from officers of the organization urging cooperation. Returns on the first (short) schedule were 78 per cent and on the second (long) schedule were 52 per cent.

Study of retired public school teachers.—A long schedule was mailed to teachers on the lists of several state and city teachers' retirement associations. In some cases the schedule was mailed by the secretary of the association with a letter urging cooperation. In most cases, however, the schedule was mailed from Chicago. The most cordial letter sent out from the office of a retirement association and urging cooperation brought 72 per cent responses from the state of Minnesota. (It is possible here that the secretary did not mail the schedule to people known to be very ill and feeble.) The coldest and least cordial letter (from New York State) brought in the lowest response, 23 per cent. The average for the study, which brought in 935 schedules, was 38 per cent.

Study of retired Methodist ministers and their widows.—A long schedule was mailed to retired Methodist ministers and widows of Methodist ministers from a sampling of Methodist conferences throughout the country. Returns averaged 27 per cent from the men and 25 per cent from the widows, ranging from a high of 58 per cent to a low of 18 per cent in various conferences for men and a high of 61 per cent and a low of 13 per cent for women. In another study, a short schedule was mailed to a sample of retired Methodist ministers from the northern and western parts of the country. Returns were 39 per cent.

Study of retired Chicago public school teachers.—A short schedule and later a long schedule were mailed out to a sample of retired Chicago public school teachers. Returns on the short schedule were 57 per cent for men and 34 per cent for women. Returns on the long schedule were 48 per cent for men and 30 per cent for women. A follow-up by interview was made, for nonrespondents still living in Chicago, with a short schedule to be filled out

during the interview. Results, expressed in percentages of nonrespondents, were:

Answered short schedule or long schedule, in response to interview	58 per cent
Moved away, too ill, or recently deceased	29 per cent
Refused	13 per cent

Study of Old Age Assistance recipients in the Woodlawn district of Chicago.—Interviewers were sent with long schedules to all people on the OAA list for this district. Results were:

Schedule completed	38 per cent
Person deceased, moved away, too ill, OAA discontinued, or could not be located with repeated calls	27 per cent
Refusals	35 per cent

From this summary of experience, it seems that the interview method is the most effective, although its results can be approached by a mailed questionnaire to a middle class professional group (teachers and YMCA secretaries) if the group is well organized and if the officers of the group will give their active approval to the project.

There has been a study of old people made recently in England which permits comparison with studies made in the United States. In the city of York, England, in 1947-1948, a survey was made of all men over 65 and all women over 60. This gave a total of 12,510 people, after excluding those who died or moved away before being visited by the interviewer(1). Of this number, a total of 1057, or 8.4 per cent, refused outright to be interviewed and another 6.3 per cent were not interviewed either because they could not be found at home with repeated calls or for other reasons. Since our Prairie City study did not use this latter category, it is perhaps fair to add them to the refusals, making 14.7 per cent. In any case, the proportion of refusals in the York Study is of similar size to that in our study.

However, only 1.1 per cent of the old people in York refused because they were too ill or feeble, while another 1.7 per cent were represented by family members who answered for them. Of those who did accept the interview, 2.1 per cent were bedridden. These facts may be taken to imply that some of our 11 per cent of subjects who did not see the interviewer ostensibly because they were too ill or feeble, were actually using this as a pretext for refusal. On the other hand, there may actually be a substantial difference between the two populations in the proportion of invalids.

In conclusion, it may be said that the experience in York, where 80 per cent of the people gave a lengthy interview, is not greatly different from our experience where 76 per cent gave an interview of similar length.

Summary

This report of experience in sampling and interviewing a representative group of people past 65 years in a typical midwestern community leads to the following conclusions:

Approximately 75 per cent of the people over 65 can be interviewed concerning their adjustment.

A group of approximately 10 per cent are too ill or too feeble to be interviewed.

A group of approximately 10 to 15 per cent refuse to be interviewed, although they are physically able to talk to an interviewer.

The groups with the most resistance to being interviewed are upper class women and lower-middle class women and men.

Interviewing is more effective than a mail questionnaire in obtaining information from older people, although the latter method approaches the interview in its effectiveness with people of middle class professional backgrounds.

The assistance of Ruth Albrecht, John Flaherty, Edith Fleming, and Marion McLaughlin, who did field work and analyzed data for this project, is acknowledged.

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Case Study Comparisons of Successful and Problem Old People

S. L. PRESSEY AND ELIZABETH SIMCOE

THIS STUDY OF 533 ELDERLY MEN AND WOMEN WAS BASED ON AN INVESTIGATION OF A GROUP OF MIDDLE CLASS OLDER PEOPLE, A SECTION WHICH HAS OFTEN BEEN NEGLECTED IN SOCIAL INVESTIGATIONS. THE CONCLUSION IS REACHED THAT THERE ARE MANY WELL ADJUSTED OLD PEOPLE IN THIS POPULATION GROUP WHOSE SUCCESS IN OLD AGE IS LARGELY BECAUSE OF THEIR MANY INTERESTS AND ACTIVITIES AND THEIR CONTINUED USEFULNESS TO OTHERS.

Most studies of old people have been of individuals in need of social or medical assistance and tending to be of lower socio-economic status. In contrast to this in the present study an attempt has been made to investigate individuals in the large middle class groups of the population and within these groups to differentiate and seek the distinctive circumstances and characteristics of old persons who might be considered well or ill adjusted. It was hoped that in this way valuable perspectives might be obtained regarding problems of aging.

Material and Methods

The method employed in gathering the data in this study may seem simple. But it is believed to have special merits. The collection of the material was made by students attending lectures on psychologic problems in adult life given by Pressey. It was proposed that each student should prepare a careful case study about one old person in his acquaintance who showed satisfactory adjustment and one individual who was a personality problem. For this purpose a simple mimeographed case-study outline was furnished, specifically asking for material on the individual's present life, active adulthood, and early years, suggesting types of information under each one of these divisions.

Success in old age was very broadly defined: there might or might not be continuing vocational usefulness or an active life; the essential was that this person be generally regarded and indeed admired as a fine old person by those who knew him. The student must know each person well or be able to obtain adequate information. Students who did not know any such old people were excused from this assignment.

Although not expert case-workers, these students had certain important advantages for the purposes of this investigation. They knew the subjects well, usually over a period of years and in terms not alone of any statements by the individual concerned, but also through information from other sources (ordinarily the person was a close relative or long-time neighbor). They generally could gather further information more easily and freely than a professional case-worker. And they could make an evaluation of each old person in terms of established family and neighborhood judgments. Most of the case reports gave evidence of these merits and the students for the most part seemed to have prepared their reports with much care.

In total, 553 useable reports were obtained, 349 (215 men and 134 women) being successful and 204 (109 men and 95 women) problem cases. Median ages were 70 for the men and 75 for the women, with range from the late fifties to the nineties. The greater number of the successful seemed an interesting indication of the frequent good adjustment to age in the socio-economic and cultural groups from which these students came. The reports were all studied and analyzed with great care by

Dr. Pressey is professor of Psychology at the Ohio State University. He received his A.B. degree from Williams College in 1912 and his Ph.D. from Harvard in 1917. Dr. Pressey is a fellow of the American Psychological Association, was first president of the Division of Maturity and Old Age of that Association, and at present is Chairman of a State Committee on Problems of the Aged in Ohio.

Miss Simcoe is a graduate student specializing in the study of psychologic problems of the older ages. She has an A.B. degree from Martha Washington College and obtained an M.A. degree from the Ohio State University in 1949.

Simcoe in an effort to differentiate factors making for success or failure in old age.

Results

The data obtained in analysis regarding the present status of successful and unsuccessful old men and women are given in table 1 in which the figures for each of the four groups are expressed in percentages. It will be noted that 15 per cent more of the well adjusted than of the problem old men lived in a small town and 19 per cent fewer in a city; the women showed similar trends. These findings are in agreement with the common notion that the easy neighborliness of a village is most favorable for old people. Also understandable is the advantage (17 per cent for the men) of remaining in old age in the same community in which the last years of the active adult life were spent.

The table includes only items of information with at least one difference over 15 per cent. For the men, living with mate was a distinctly favorable circumstance; living alone or in an institution was not, for either sex. For both sexes, good health, financial security, and church attendance were important. Especially distinctive (showing differences over 40 per cent) were four characteristics: (1) the successful of both sexes were not idle—they were either employed or doing useful things even if not for pay, (2) they were much more likely to have active social relationships, (3) they had many more abilities—such as in music, gardening, cooking, or handicraft, and (4) most differential of all (65 per cent or more) were the many and diverse interests of the successful.

These last four findings would seem in striking support of current efforts to help old people find usefulness of some sort, to maintain or develop abilities of possible value to them, and in particular to retain or establish many and varied interests and social relationships.

Table 2, regarding the earlier active adult life, supports the findings shown in table 1, but the differences are less marked; again only items with at least one difference over 15 per cent were included. Men who had spent their active adult years in a city seemed less likely to find a happy old age than those who had lived in a small town or in the country. For both sexes, good health, church attendance, and many social interests in the middle years were favorable to a successful old age. Not so clearly significant and therefore not included in the table were financial status during the active adult years (although 9 per cent more of the successful men were comfortable financially and 8 per cent less were poor). Age at death of parents did not seem to make a difference and was not included in most reports.

As would be expected (table 3), evidence regarding the childhood and adolescence of these old people was inadequate but tended to be in support of the trends already mentioned. Proportionately more problem cases came from a childhood spent in a city. A comfortable home seemed to be better than either poverty or wealth. Although for the most part data were lacking, moderate rather than either strict or lax discipline in the home and a church-attending family were found to have been favorable. The amount of education seemed to have been not at all differentiating for the men; however, 14 per cent more of the successful women had attended college and 7 per cent fewer had been to elementary school only. Also showing little differentiation was the number

TABLE 1. PRESENT STATUS.

Percentages of 215 successful and 109 problem old men and 134 successful and 95 problem women having the indicated characteristics, also percentage of difference between groups (differences in the direction of the maladjusted group are preceeded by a minus sign).

Characteristics	Men			Women		
	Successful	Problem	Difference	Successful	Problem	Difference
Environment						
Rural	8	5	3	5	3	2
Small Town	29	14	15	28	16	12
City	56	75	−19	65	78	−13
No Data Given	7	6	1	2	3	−1
Same as Last 20 Years*	71	54	17	48	45	3
Living With						
Mate	50	29	21	19	20	−1
Children	10	14	−4	31	35	−4
Siblings	1	3	−2	6	11	−5
Friends	3	6	−3	11	3	8
Alone	9	20	−11	21	25	−4
Institution	1	9	−8	2	6	−4
No Data Given	26	19	7	10	0	10
Health						
Good	68	36	32	67	28	39
Fair	16	16	0	20	34	−14
Poor	13	44	−31	11	38	−27
Financial Position						
Rich	9	2	7	4	4	0
Comfortable	89	62	27	94	87	7
Poor	1	32	−31	1	8	−7
Marital Status						
Single	1	18	−17	12	19	−7
Mate Living	51	36	15	19	22	−3
Mate Deceased	22	24	−2	63	53	10
Divorced	3	14	−11	6	5	1
No Data Given	27	40	−13	18	25	−7
Married, no Children*	4	22	−18	19	29	−10
Work Status						
Gainfully Occupied	41	28	13	20	9	11
Doing Useful Work	53	18	35	78	49	29
Idle	4	51	−47	1	41	−40
Church Attendance						
Often	31	9	22	42	20	22
Occasionally	7	1	6	9	6	3
Never	3	10	−7	0	12	−12
No Data Given	59	80	−21	49	62	−13
Social Relationships						
Active	80	17	63	86	19	67
Retiring	16	77	−61	12	80	−68
Interests						
Many	90	17	73	91	28	65
Few	7	77	−70	7	72	−65
Abilities						
Many	85	21	64	87	24	63
Few	10	74	−64	10	75	−65

* "No Data" percentages are omitted when none are over 6 per cent; also omitted are the obvious alternatives ("changed" and "no children") of the starred items.

TABLE 2. ACTIVE ADULT YEARS.

Percentage evaluation of each group having the indicated characteristics.

Characteristics	Men			Women		
	Successful	Problem	Difference	Successful	Problem	Difference
Environment						
Rural	15	10	5	15	15	0
Small Town	25	16	9	22	21	1
City	53	69	−16	62	60	2
No Data Given	7	5	2	1	4	−3
Health						
Good	88	71	17	87	73	14
Fair	6	18	−12	6	20	−14
Poor	1	6	−5	2	4	−2
Church Attendance						
Often	37	10	27	51	28	23
Occasionally	4	1	3	1	3	−2
Never	1	9	−8	0	5	−5
No Data Given	58	80	−22	48	64	−16
Social Interests						
Many	58	9	49	70	20	50
Few	24	74	−50	17	66	−49
No Data Given	18	17	1	13	14	−1

of siblings, although 5 per cent more of the problem old men and 7 per cent more of the problem old women had been only children.

Old people who had spent their childhood in the country, been neither rich nor poor, came from church-attending families of moderate size, were probably most often at home in our culture and of strong family loyalties. These last two factors may have been the important ones; but the total consistency of all the findings seems of great interest.

Since continuing usefulness and many abilities and interests were found especially characteristic of success in old age, an inventory of vocational and avocational activities and interests of the successful seemed of value. Table 1 showed that 41 per cent of the 215 successful men and 20 per cent of the 134 successful women were gainfully occupied in some way. Of the men, 6 per cent farmed, 4 per cent ran a store, 3 per cent each were in factory work, retail selling, or business management; 2 per cent each listed themselves as teachers, clergymen, or engineers. Of the women, 3 per cent each were teaching, renting rooms, or serving as house mothers. Scattered occupations for the men ranged from janitor and bartender to superintendent of schools and bank president; among occupations mentioned by the women were taking care of an invalid, restaurant work, and statistical work.

The total (272 for the men and 250 for the women) and the variety of the nonpaid activities of some usefulness to others mentioned by the successful men and women makes an impressive display of the possibilities of service in the older years. Table 4 shows activities engaged in by 5 per cent or more of the successful groups. The interest in young people is to be noted, and the frequent mentioning of housekeeping and needlework indicates that women find more opportunities for usefulness in the older years than men. Scattered activities for the men included clerking in a store, painting a house, serving as member of a school board and on the board of a summer camp, keeping a pony for neighbor children to ride, and local news broadcasting; the women mentioned taking care of an invalid, caning chairs, making rag rugs, and rolling bandages.

The suggestion is ventured that it might be worth while to compile a classified list of

TABLE 3. CHILDHOOD AND ADOLESCENCE.

Percentage evaluation of characteristics of group studied.

Characteristics	Men			Women		
	Successful	Problem	Difference	Successful	Problem	Difference
Environment						
Rural	39	28	11	46	29	17
Small Town	35	30	5	32	34	−2
City	18	30	−12	17	28	−11
No Data Given	8	12	−4	5	9	−4
Family Financial Status						
Rich	3	10	−7	7	11	−4
Comfortable	70	54	16	79	68	11
Poor	22	23	−1	10	14	−4
No Data Given	5	13	−8	4	7	−3
Health						
Good	90	75	15	89	79	10
Fair	3	7	−4	4	5	−1
Poor	2	7	−5	1	11	−10
No Data Given	5	11	−6	6	5	1
Amount of Education						
College	28	26	2	24	10	14
High School	26	26	0	31	35	−4
Elementary	37	30	7	25	32	−7
No Data Given	9	18	−9	20	23	−3
Discipline in Home						
Strict	24	23	1	19	29	−10
Moderate	20	11	9	21	8	13
Lax	1	17	−16	3	7	−4
No Data Given	55	49	6	57	56	1
Church Attendance						
Often	51	21	30	61	45	16
Occasionally or Never	4	9	−5	3	3	0
No Data Given	45	70	−25	36	52	−16

TABLE 4. USEFUL ACTIVITIES.

Percentages of 125 successful old men and 134 successful old women who engaged in the following activities useful to others.

Activities	Men	Women
Church	24	29
Gardening	21	19
Carpentry	17	—
Housework	4	43
Needlework	4	36
Fostering Activities of Young People	16	25
Civic Groups	14	9
Lecturing	6	—
Telling Stories	6	—
Helping Young People Financially	5	6
Miscellaneous	13	22

Since many persons engaged in more than one activity, percentages total more than 100.

renumerative and nonrenumerative work in which old people have engaged, for the use of other old people.

Table 5 shows activities engaged in by 5 per cent or more of the successful men and women for their own amusement. The variety of miscellaneous activities is great. The men mentioned study of British history, collecting antiques, building an outdoor fireplace, remodeling an old house, trap shooting, pingpong, billiards, bicycling, riding a motor cycle, training a horse, and horseback riding. The total list included 30 different recreations. The women's list included making shell pins, compiling geneologies, composing songs, fishing, horseback riding, and dancing.

To give a concrete picture of the ways these various types of data aggregate in a given case,

TABLE 5. RECREATIONAL ACTIVITIES.

Percentages of 215 successful old men and 134 successful old women who engaged in the following activities for their own amusement.

Activities	Men	Women
Visiting Friends	30	42
Reading	32	44
Clubs	21	15
Traveling	17	18
Sports—spectator	15	—
Fishing	11	1
Playing Cards	10	8
Radio	10	17
Politics	9	3
Listening to Music	7	4
Hunting	7	—
Movies	6	11
Golf	6	—
Playing Musical Instrument	4	5
Writing Letters	1	10
Miscellaneous	40	31

brief summaries follow of one successful and one problem case. As indicative of the adequacy of some reports, it may be mentioned that the full report in the first case was 2500 words long.

A successful old man of 75.—Sources of information: known by the student for about 20 years; information from him direct and also from a close friend and associate. Born one of five children on a farm in Pennsylvania, his family moved to Kansas and then to Iowa. The family was active in the country social gatherings at church and school and was musical (all sang and played some musical instrument); the family life was very happy. The subject went fishing and hunting with a brother and neighbor boys; health was good and physical growth rapid; at 16 he entered a small college, preparing to teach.

Thereafter for several years he taught and took further schooling, finally completing a degree in accounting. He married immediately after graduation from college and had two children. He managed a business school and also developed a forty acre apple orchard and by means of continuing study became a leader in his state in horticulture. Throughout his adult life he has been active in church work; he has sung in the choir and played cello in a local orchestra; he has been a leader in the community—is a member of Rotary and was twice on city council.

His wife's death when he was 72 was a great loss. But he is continuing an active life in church and community, visits with friends, has a large correspondence, frequently helps young people in various ways, has many hobbies, the most outstanding being a collection of material about Abraham Lincoln. He is often called on to give lectures about Lincoln and also on horticulture. Although comfortable financially, he is still gainfully occupied about ten months of the year helping make out income tax returns, spraying orchards, selling farm equipment, surveying, lecturing; the other two months he takes trips, visits a brother in Florida.

A problem woman, age 60.—Known through neighborhood contacts for many years; information obtained from the subject, a daughter, and a neighbor. She was born and raised in a small coal mining area where the grandfather was an immigrant miner. The parents were strict and frugal to the point of begging on the part of the father, much to the embarrassment of the children. She had three brothers and three sisters; the family was and still is a quarrelsome group. The subject went through high school earning her own way and felt inferior to other girls. She was then a telephone operator for awhile but was not liked by the others.

When 22 she married a miner, but was ashamed that he was not a white-collar worker and ever since has nagged and criticized him; now risen to mine foreman, he has a comfortable income which she spends freely but considers inadequate. The one daughter was dominated by her and finally after a quarrel over her choice of career (nursing) left home—quietly aided by her father.

She chronically complains of vague ailments, for which medical examination shows no basis. She does not get on well with neighbors, whose sympathies are with the husband and daughter, and has few contacts except through attendance at church. She is highly intolerant of minority groups (perhaps a product of her shame of her immigrant parentage) and very opinionated. Now increasingly hypochondriac, estranged from her daughter, bitter at her husband, and angry at the neighbors, she is a problem to her family and herself.

The contrast between these two people in early home influences, adult life, and traits in old age is surely marked. Particularly distinctive is the continued effort at usefulness and friendly helpfulness and the wide range of active social interests of the first person and the contrasting increase with age in estrangement and demandingness of the second.

DISCUSSION

In looking over the study as a whole, four points seem important.

1. The possibility of gathering valuable information regarding certain types of problems

through college classes informed about these problems is demonstrated. To have studied so many cases in so many communities as adequately and appraised them as broadly by means of field workers would have been difficult and expensive.

2. It seems evident that in the great middle classes of the population there are many individuals who make decidedly successful adjustments to old age. Bereavements, infirmities, and losses of means and of status crowd in upon them; yet they attain a cheerful courage, thoughtfulness of others, and wide usefulness. Preoccupation with unfortunates in institutions or agency offices may lead to underestimation of the potentialities of the aged or the number who are truly successful in their last years.

3. A study of such well adjusted old people would seem necessary for adequate empirical determination as to what makes for success in old age. And when they are contrasted with cases from the same relatively favored classes who nevertheless became problems, the distinctive factors making for success should emerge. Such study shows that success in old age tends to be founded upon and developed from wise living before old age comes. Good sense about health and some range of interests and abilities in maturity make for a good adjustment in old age.

However, not all the successful old people had such backgrounds, and some who did were more successful in old age than others. Certain steps tending to make old age better can be taken by almost any old person. He can try to be useful, to develop interests and abilities suitable to his condition and circumstances, and to find friends. And those trying to help the aged can help them do these things. Values of sheltered workshops, Golden Age Clubs, and recreational programs for the elderly are thus emphasized. There is nothing new in all this. But certain differentiating factors which makes for success or failure in old age are very clearly brought out and might well be helpful to other old people.

4. The cases as personality totals suggest more than a sum of such activities, however; the most successful old individuals exhibit a philosophy of life and a certain related mellowed quality of character which seemed of special importance. They sturdily believed in continued usefulness; their own careers being over, they found their satisfaction particularly in service to others; their greater free time was seen as an opportunity for more friendliness. The unfortunateness of the cultural convention that old age is a time of selfish idleness and the importance of developing such positive philosophy in old people are thus stressed as basic orientations.

Summary

In contrast to studies of aged individuals who are ill, in institutions, or in economic need, this investigation has attempted to study vigorous old people of good socio-economic status who were considered by those who knew them well to be successful in their adjustment to old age and to contrast them with individuals of the same general socio-economic classes who were problems.

Data were gathered through students in university classes training in case study methods and orientation regarding problems of age; a total of 349 successful and 204 problem cases were dealt with. It is believed that exceptionally adequate material and satisfactoriness of appraisal as to success or failure was obtained.

The methods of handling the material included detailed tabulation of the frequency of various circumstances and characteristics in the successful and problem groups for each sex, the conversion of these data to percentages, and the location of items showing greatest differences.

Especially differential of the successful people were their continuing usefulness, their many social relationships, their maintaining various abilities, and their lively and varied interests. Detailed study of the people yielded lists of occupations and service work which old people had found they could manage and of hobbies, abilities, and interests which they had

found most feasible and helpful in maintaining good adjustment in old age. Basically most differential of the successful was the active outgoing philosophy of life.

The findings emphasize the value of certain current efforts to help the aged, give concrete suggestions as to ways in which these efforts may be carried forward, and stress particularly needed changes in conventional opinion regarding old age.

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HISTORICAL SECTION

SEBASTIAN BRANDT (1457-1521) — lawyer, town-clerk of Strasbourg, and poet, is famous for "Das Narrenschiff" (The Ship of Fools), the great satirical and didactic poem. The wood-cut shown above is from the contemporary English translation and vividly illustrates the infirmities of old age by showing an elderly man with one foot actually in the grave.

F. D. Z.

CURRENT COMMENT

California Changes Its Mind

Californians went to polls in November, 1949, and emphatically repealed the drastic changes in the old age pension set-up which had been written into the State Constitution the previous year by a scanty margin of 37,282 votes out of 3,638,318 cast. Monthly grants had been increased to $75.00, personal property restrictions had been liberalized, the relatives of indigent persons were relieved of all responsibility for their support, and the minimum age of pensioners was reduced from 65 to 63 years. In addition the State Director of Social Welfare was made an elective office.

The repeal denies pensions to persons 63 and 64 years of age and will remove 18,000 persons from the case load. Clauses forcing limited responsibility on relatives and lowering the amount of property and insurance a pensioner may have will eliminate 23,000 more. The State will thereby save about $65,000,000 annually.

The situation caused by the 1948 vote had caused alarm not only in California but throughout the nation because of its serious implications. *Life,* in its October 17, 1949, issue, devoted five pages of text and photographs to the "Battle for Pensions," pointing out that the coalition favoring repeal was made up of the League of Women Voters, the Chamber of Commerce, and the Parent-Teacher Association, which argued that increased pensions were endangering school funds and other welfare projects.

The current set-back for those favoring liberal payments to the aged serves to highlight the other ways in which the ideal of social security may be attained and to emphasize the need for industry to take the lead in abolishing compulsory retirement ages and in keeping healthy old people gainfully employed according to their functional capacity.

News and Notes

The Fourth Annual Hobby Show for Older Persons, sponsored by the Welfare Council of New York City, will be held from May 4 through May 14 at the American Museum of Natural History, 77 Street and Central Park West, between 10 A. M. and 5 P. M. daily and 1 P. M. to 5 P. M. on Sundays.

This exhibit will show the work of New Yorkers 60 years and older and there will be a wide variety of exhibits. Older persons whose hobbies are singing, dancing, music, and other forms of entertainment will have an opportunity to perform.

Those who are interested in exhibiting should write or telephone for an entry blank to the Hobby Show for Older Persons, 44 East 23 Street, New York 10 (Algonquin 4-5500). There is no entrance fee.

The Hobby Show, first organized by the Welfare Council in 1947, has grown each year;

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The hieroglyphics, "The Beginning of the Book for Transforming an Old Man into a Youth," at the top of this editorial page, are from the Edwin Smith Surgical Papyrus, translated by Professor John Breasted, University of Chicago Press.

last year there were about a thousand exhibitors.

The Institute for Human Adjustment, in cooperation with the Extension Service of the University of Michigan, has announced the Third Annual Institute on Living in the Later Years, to be held in Ann Arbor, Michigan, June 28, 29, and 30. The program is as follows:

Mental Health Problem of an Aging Population
Mental Health in the Aging Population
Changes in Emotional Needs with Aging
Psychiatric Techniques in the Treatment of Older People
Medical Problems of an Aging Population
Chronic Disease and Its Control in Older Persons
Community Health Services for Older People
The Industrial Physician and the Older Worker
Physical Restoration for the Aging
Education for an Aging Population
Responsibility of Education to the Older Adult
Proposed Programs in Education for an Aging Population
Training for Volunteers in Community Services with Older People

In addition there will be three special addresses, four organized discussion groups, and a demonstration of an activities center for older people. Persons interested in attending are invited to write to the University of Michigan Extension Service, 4524 Administration Building, Ann Arbor, Michigan, for further information.

In order to stimulate the formation of a well-rounded program for the prevention and control of chronic disease and for the care and rehabilitation of the chronically ill, the Commission on Chronic Illness was organized last year under the sponsorship of the American Medical Association, the American Hospital Association, the American Public Health Association, and the American Public Welfare Association. Dr. Morton L. Levin, assistant commissioner for medical services of the New York State Department of Health, has been appointed director of the Commission, which will have its office at the headquarters of the American Medical Association in Chicago.

Massachusetts old age recipients became eligible in December, 1949, for an extra $4.00 monthly allowance for leisure time activities, making Massachusetts the only state to make legal provision for recreation for the aged. On the basis of the October figures, Massachusetts' old age benefits are the highest of any state east of the Rocky Mountains. Massachusetts is one of twenty-seven states which include in old age payments money for church and club membership as well as personal incidentals. Additional benefits include a $10.00 a day allowance for hospital expenses, when incurred.

The First Internation Conference of Gerontological Societies will be held in Liège, Belgium, July 9-12 instead of July 10-13 as previously announced. The Conference is sponsored by the Belgian Gerontological Group of which Dr. L. Brull, Hospital Bavière, Liège, Belgium, is the president. As many as five delegates from each Gerontological or Geriatrics Society will be recognized. The committee representing the American Gerontological Society consists of A. J. Carlson, E. V. Cowdry (Chairman), R. A. Moore, A. I. Lansing and N. W. Shock.

All Gerontological and Geriatric Societies throughout the world are invited to send official representatives to present papers. Representatives of other organizations engaged in gerontologic research will likewise be welcome. In addition to the presentation and discussion of the results of gerontologic research it is the purpose of this international conference to establish an International Union of Gerontological Societies and to promote the financing of research in this subject throughout the world. For information write either to Dr. L. Brull or to Dr. E. V. Cowdry, Washington University School of Medicine, St. Louis 10, Mo.

ORGANIZATION SECTION

C. J. Van Slyke, *President*
National Heart Institute
National Institutes of Health
Bethesda 14, Maryland

Henry S. Simms, *Secretary*
630 W. 168th Street
New York, New York

John Esben Kirk, *Treasurer*
5600 Arsenal Street
St. Louis 9, Missouri

Robert A. Moore, *President-Elect*
507 S. Euclid
St. Louis 10, Missouri

Financial Reports

GERONTOLOGICAL SOCIETY, INC.

Membership Account

For the year ended December 31, 1949

Balance January 1, 1949			$ 1,320.29
Receipts:			
Memberships	$ 709.10		
Subscriptions	2,825.00		
Partial Reimbursement for First Scientific Meetings	546.00		
Total Receipts		$ 4,080.10	
Disbursements:			
Transferred to Journal Account	2,903.00(a)		
First Scientific Meeting (New York)	1,320.49		
Second Scientific Meeting (Chicago)	475.46		
American Registry of Gerontology	200.00		
Printing and Stationery	155.00		
Postage	57.47		
Telegrams	2.62		
Refunds	12.00		
Total Disbursements		5,126.04	
Excess of Disbursements			1.045.94
Balance December 31, 1949			$ 274.35

(a) An additional $78.00 was transferred for the 1949 subscriptions paid in 1948 because of the change in price of the Journal subscriptions to members.

GERONTOLOGICAL SOCIETY, INC.
Journal Account
For the year ended December 31, 1949

Balance January 1, 1949			$ 9,970.12
Receipts:			
Subscriptions	$ 8,895.89		
Advertising	2,867.76		
Reprints	1,110.96		
Engraving	120.83		
Total Receipts		$12,995.44	
Disbursements:			
Printing and Mailing Journal	10,435.25		
Reprints	842.46		
Shipping and Postage	396.64		
Travel Expense	336.97		
Publicity	263.83		
Stationery and Printing	146.88		
C. C. Thomas for 1946 Back Issues	85.60		
Copyrights	24.00		
Office Supplies	23.40		
Telephone and Telegrams	15.42		
Refunds	12.65		
Total Disbursements		12,583.10	
Excess of Receipts			412.34
Balance December 31, 1949			10,382.46
Recapitulation:			
Cash in Bank			10,362.23
Petty Cash on Hand			20.23
			$10,382.46

GERONTOLOGICAL SOCIETY, INC.
Editorial Account
For the year ended December 31, 1949

Balance January 1, 1949			$ 2,124.84
Receipts:			
Josiah Macy, Jr. Foundation	$ 3,000.00		
Total Receipts		$ 3,000.00	
Disbursements:			
Accounting Service	30.00		
Typewriter Rental	35.00		
Salaries	3,710.40(a)		
Office Equipment	27.50		
Book	3.60		
Total Disbursements		3,806.50	
Excess of Disbursements			806.50
Balance December 31, 1949			1,318.34
(a) Total Salaries for Period			3,600.00
Plus: Taxes withheld but not remitted until this period:			
Federal Income Tax		109.50	
City Income Tax		6.00	115.50
			3,715.50
Less: City Income Tax withheld but not remitted as of Dec. 31, 1949		4.50	
3% Collection Fee		.60	5.10
			$ 3,710.40

1949 ANNUAL REPORT OF THE MEMBERS OF THE GERONTOLOGICAL SOCIETY, INC., PURSUANT TO SECTION 46 OF THE MEMBERSHIP CORPORATIONS LAW OF NEW YORK

TO THE MEMBERS OF THE GERONTOLOGICAL SOCIETY, INC.:

The members of the corporation submit the following report for the year ended December 31, 1949.

(1) Real property		$ 0.00	$ 0.00
Personal property			
Cash deposit in the First National Bank:			
Editorial Office Account		1,318.35	
Membership Account		274.35	
Cash deposit in Boatmen's National Bank:			
Journal Account		10,382.46	
Petty cash fund		20.23	
Office furniture (St. Louis)		100.00	
Estimated value, back issues of the Journal of Gerontology, 1947, 1948, and 1949 (St. Louis)		6,000.00	
Total			18,095.38
(2) Receipts: The amount and nature acquired during the year ended December 31, 1949:			
Grant from Josiah Macy, Jr. Foundation		3,000.00	
Membership dues		709.10	
Subscriptions to Journal of Gerontology		8,895.89	
Advertising, reprints, excess engraving in Journal of Gerontology		4,099.55	
Total			16,704.54
(3) Disbursements: The amount applied, appropriated or expended during the year ended December 31, 1949:			
Printing and mailing Journal		10,435.25	
Reprints		842.46	
Shipping and postage		454.11	
Travel expense		336.97	
Publicity		263.83	
Stationery and printing		301.88	
Charles C. Thomas for 1946 issues of the Journal of Gerontology		85.60	
Copyrights		24.00	
Office supplies		54.00	
First Scientific Meeting		774.49	
Second Scientific Meeting		475.46	
American Registry of Gerontology		200.00	
Telephone and telegrams		18.04	
Refunds		24.65	
Accounting service		30.00	
Typewriter rental		35.00	
Salaries		3,710.40	
Total			18,066.64
(4) Summary			
Cash balance on hand January 1, 1949		13,415.25	
Receipts during year ended Dec. 31, 1949		16,704.54	
Disbursements during such year		18,066.64	
Leaving a balance of			12,053.12

(5) The names and places of residence of the persons who have been admitted to membership in the corporation during the year ended December 31, 1949:

(1) Dr. C. J. Van Slyke
National Heart Institute
National Institutes of Health
Bethesda 14, Maryland
(2) Dr. Oliver H. Lowry
Department of Pharmacology
Washington University
School of Medicine
St. Louis 10, Missouri
(3) Mr. George E. Johnson
522 Fifth Avenue
New York 18, New York

Dated January 31, 1950

State of Missouri }
City of St. Louis } ss.

Clive M. McCay and Robert A. Moore, being severally duly sworn, each for himself says: That the said Clive M. McCay was President, and that the said Robert A. Moore was Treasurer of the Gerontological Society, Inc. for the year 1949; that the foregoing is a report thereof showing the whole amount of personal property owned by said corporation, where located, and where and how invested; the amount and nature of the property acquired during the year ended December 31, 1949, being the year immediately preceding such date, and the purpose, objects, or persons to or for which such applications, appropriations, or expenditures have been made; the names of the persons admitted to membership in the corporation during the year; and that the corporation owns no real property; which report is in all respects true to the best of deponents' knowledge and belief.

CLIVE M. MCCAY, *President*
ROBERT A. MOORE, *Treasurer*

Irish Gerontologic Activities

The first legislation directed to the care of the aged in Ireland was contained in the pre-Christian Brehon laws. Three items of maintenance were allowed to the aged person: for maintenance in food, half a wheaten loaf with salt and a vessel of sour milk daily; for attendance, his body to be washed every twentieth night and his head every Saturday; for milk, the product of a milch cow every month throughout the year. Houses for poor aged men were to be at least 17 feet long and made of basket work with weather boards.

For many centuries the care of the aged poor devolved upon charitable religious and lay bodies. At the time of the great famine in 1847 workhouses were opened throughout the country and served as the last refuge of many a poor old person.

With the foundation of the Irish Free State in 1922 the workhouses were renamed county hospitals or homes and efforts were made to segregate the aged sick and those whose disability was financial rather than physical. Apart from this, little was done until the present year (1949) when several geriatric advances and investigations were set on foot independently and simultaneously.

In Belfast, the old Convalescent Block of the City Hospital has been converted into a Geriatric Unit with 400 beds under the charge of Dr. G. Adams, who is also undertaking a survey on the question of the care of the elderly in the North of Ireland. This latter work is being done in conjunction with the Department of Social Medicine of Queen's University, Belfast. It is hoped that shortly the buildings will be fully adapted so as to provide a rehabilitation and follow-up unit for the elderly and chronic sick wards for the same age group.

At the autumn meeting of the Irish Division of the Royal Medico-Psychological Association the principal item was a paper read by Dr. C.

B. Robinson on The Aged in Mental Hospitals. His most significant point was that approximately one-third of the people over 60 years of age confined in mental hospitals are fit for discharge to residential homes where minimal nursing would be obtainable. Owing to the lack of these homes some 600 elderly patients must be unnecessarily retained in mental hospitals.

In the South of Ireland, Dr. John Fleetwood is conducting a survey of healthy old age pensioners in order to establish physiologic norms for the later age groups. He has also presented a paper, Problems of Old Age in General Practice, to the Medical Society of University College, Dublin.

The President of the Biological Society of the Colleges of Physicians and Surgeons in Ireland, Mr. T. A. Bouchier-Hayes, chose Geriatrics for the subject of his inaugural address. His Excellency, Mr. G. Garrett, the United States Minister to Ireland, spoke about the paper from the layman's point of view.

The present old age pension rates in the South of Ireland are low, about $150.00 per year for those aged 70 or over. A White Paper recently issued by the Department of Social Welfare proposes to increase the benefits to $175.00 payable at age 65 for men and 60 for women.

Throughout the various surveys and discussions three facts stand out clearly: (1) The problem is growing. People over 65 years of age account for 10 per cent of the population instead of 3 per cent as they did a hundred years ago. (2) Medical and nursing personnel must be taught that rehabilitation of the elderly is interesting and productive of good results. (3) There must be more accommodation for those old people who require minimal nursing attention.

JOHN FLEETWOOD

THIRD ANNUAL MEETING
of the
GERONTOLOGICAL SOCIETY

St. Louis, Missouri
November 12 and 13, 1950

HEADQUARTERS - CHASE HOTEL

PLEASE MAKE YOUR RESERVATIONS EARLY

GERONTOLOGIC REVIEWS

THE URINARY SEDIMENT COUNT IN OLD AGE

Since the introduction in 1925 by Addis (Journal of the American Medical Association, *85:* 163-167, 1925) of a method for quantitative evaluation of the excretion of formed elements in the urine, this sediment count has been used quite extensively, especially in clinical research on nephritis and allied conditions. The first publications dealing with Addis' method of urinary sediment counting brought out the important fact that both red blood cells, casts, and epithelial cells must be considered as normal constituents of the urine, so that the difference between normal and pathologic urine samples is a quantitative rather than a qualitative one.

The 12-hour excretion values found in normal young individuals by Addis (Journal of Clinical Investigation, *2:* 409-415, 1925-1926), Goldring (Journal of Clinical Investigation, *10:* 354-367, 1931), and Næraa (Kvantitative Urinsedimentbestemmelser. A. Busck, Copenhagen, 1936) are tabulated below and are in good agreement.

In contrast to the adequate studies in younger subjects, results of complete urinary sediment counts with Addis' technique in elderly individuals have only been reported by Næraa (Kvantitative Urinsedimentbestemmelser. A. Busck, Copenhagen, 1936), who studied a group of 10 men between 65 and 90 years of age. These men were apparently healthy as judged by a thorough clinical examination, and their urines gave no protein reaction with Heller's test. The investigation revealed a mean 12-hour excretion of 759,000 red blood cells, 814,000 white blood cells and epithelial cells, and 8140 casts. These findings are most interesting since they show an excretion of red blood cells about 6 times higher than in the young subjects and an excretion of casts about 4 times higher.

12-Hour Excretion Values

Author	No. of Subjects	Red Blood Cells	White Blood Cells and Epithelial Cells	Casts	Comments
Addis	74	65,750 (0-425,000)	322,500 (32,400-1,835,000)	1,040 (0-4,270)	Medical Students
Goldring	45	163,000 (0-1,530,000)	647,000 (24,000-3,400,000)	647 (0-9,200)	Medical Students
Næraa	70	130,000 (0-1,100,000)	1,000,000 (48,000-4,000,000)	1,900 (0-8,700)	Normal Individuals aged 20-40 years

The demonstration of a higher number of red blood cells in the urinary sediment is not commented on by Næraa, whereas the abnormally high excretion of casts as compared with the younger age group is attributed to the presence of arteriosclerotic changes in the kidneys in old age. In this connection Næraa calls attention to the fact that arteriosclerotic changes are often found at autopsy in the kidneys of old people who during life had not shown clinical signs of renal lesion.

In a recent publication Chieffi and Kirk (Journal of Nutrition, *37:* 67-79, 1949) reported the results of counts of the urinary excretion of epithelial cells in 34 men and 31 women between 50 and 99 years of age. Since only an investigation of the correlation between

the plasma vitamin A value and the excretion of epithelial cells in the urine was attempted, counting of the other formed elements in the sediment was not undertaken. None of the patients included in the study suffered from urinary infection or nephritis. The samples in the women were obtained by catheterization, whereas the urine from the men was collected directly in clean bottles.

The results showed an average 12-hour excretion of 6,400,000 epithelial cells in the men and 6,100,000 cells in the women. These values are considerably higher than the mean figure of 840,000 observed by Næraa in his study of 10 old men, especially when it is considered that Næraa's values include both epithelial cells and white blood cells.

These interesting features brought out by the rather scanty observations in old subjects should encourage further research in this field. In contemplating sediment counts in old individuals it should be recalled that many elderly persons are addicted to the use of salicylic acid preparations for rheumatic complaints and that such preparations, as emphasized by Næraa, probably by causing a precipitation of mucinous material in the renal tubules may condition a severalfold increase in the excretion of casts which is not indicative of any renal lesion.

JOHN ESBEN KIRK

BOOK REVIEWS

HANDBOOK OF CARDIAC AND PULMONARY DISORDERS

PHYSIOLOGY IN DISEASES OF THE HEART AND LUNGS, M. D. Altschule, Harvard University Press, Cambridge, Massachusetts, 1949, 368 pages, $5.00.

According to the author's preface, this monograph was written at the request of third and fourth year students at the Harvard Medical School, but Dr. Altschule also realizes how useful his work may be for the practicing physician. The reviewer, who was trained in a day when quantitative clinical methods were only beginning to be known, has found much to interest him in this work of applied physiology.

Actually the greater part of the book is devoted to cardiac disorders, something less than a hundred pages being concerned with pulmonary diseases. Breaking up the topics into smaller parts, with comprehensive bibliographies, makes for easy reading. Theoretic conceptions are minimized and actual observations given first place by avoiding all details of method. The author is able to present in succinct form the results of many investigators and at times to reconcile conflicting points of view. The references are well chosen and guide the reader through the labyrinths of medical literature.

As a working handbook to be used in conjunction with clinical textbooks, this volume by an active investigator will surely find wide acceptance among students of medicine, whether still in the classroom, or actively endeavoring to treat the sick with the best that modern science has to offer.

F. D. ZEMAN

HOUSING THE DEPENDENT AGED

FIT SURROUNDINGS, Robert H. Kirkwood, Department of Public Welfare of Virginia, Richmond, 1948, 174 pages, paper bound, (limited number available for free distribution).

This is a report of the legal developments and of the organization and administration of district homes for the aged in the State of Virginia. District homes are consolidations of county homes or county almshouses and have for their purpose more effective administration and care of aged people than was possible in the small county poor farms. While permissive district home legislation was passed in 1918, the first such home was not opened until 1927. There are four district homes in Virginia now, but the geographic areas covered still represent only a fraction of the State, roughly speaking about one-third.

The homes are an improvement over the smaller county-type of institutions for the care of the destitute aged, but they still do not meet the needs. Generally, a person must be in good health to be admitted to one of the homes, whereas the need as expressed by county welfare workers is a type of institution that will take care of the partially sick or of those who need some kind of medical care on a more or less permanent basis. The district homes are an improvement but hardly a solution to the problem of housing for the aged. They have many of the same problems of the

old county homes, such as the inefficiency resulting from the separation of whites and Negroes, lack of adequate personnel, lack of medical care, lack of recreation and interest programs, and isolation.

The report is an interesting statement of the development of these district homes and it includes some important data on the operation of the homes. There is a slight attempt to over-sell the development. The title Fit Surroundings is somewhat misleading; the shortcomings and deficiencies of the district homes are actually outlined in the concluding chapters of the report. "Toward More Fit Surroundings" would be a more appropriate title.

Students of the problem of housing the dependent aged will want to read this report of one experiment. To get a rounded picture, however, the reader should supplement the Virginia report with other material and reports of other experiments of housing and giving services to the dependent aged.

B. E. YOUNGDAHL

RELIGION AS A FACTOR IN ADJUSTMENT

RELIGION AND OLD AGE, A Study of the Possible Influence of Religious Adherence on Adjustment, Eva S. Oles, 1949 (53 page typewritten thesis, Dept. of Psychology, Bucknell University, Lewisburg, Pennsylvania).

The purpose of the investigation was to determine to what extent, if any, religion affected the adjustment of old people. The study was confined to orthodox Jewish people, evenly divided as to sex, all over the age of 65 (average age 78). Twenty-eight of the subjects were institutionalized, 10 lived in homes of their own, a total of 38. The institutionalized subjects were from two Jewish Homes for the Aged in New York City.

A questionnaire of 21 queries, 13 relating to adjustment and 8 to religion, was set up. The questions were put to the individuals by the investigator after a state of rapport was established. Each subject was interviewed privately, and many of the questions were rephrased and asked a second time so that as accurate an answer as possible could be obtained. The questionnaire was not used by the subject but served as a guide to the investigator. Two aspects of the subject's life were examined, the degree of religious adherence and the degree of adjustment.

The data obtained were separated into four sections in each category: in religious adherence, intensely, fairly, somewhat, and none; in adjustment, well, fair, poor, and very poor.

An analysis of the data indicated that:

1. In the well adjusted group, there were no nonreligious, all being in the intensely or fairly religious sections.
2. In the fairly adjusted group, 75 per cent were in the intensely or fairly religious sections.
3. In the poor and very poorly adjusted groups, only 35 per cent were intensely religious or fairly religious.

There were no significant differences found between those who were in institutions and those in their own homes. No differences in the degrees of adjustment or of religious adherence were found as existing between the sexes. An interesting by-product was found to indicate that those with poor health were more inclined toward religion than those in good health.

The conclusion seems to be that the greater the degree of religious adherence of the oldster, the better his apparent adjustment.

W. D. BLAKE

ANALYSIS OF THE LIFE TABLE

LENGTH OF LIFE, A STUDY OF THE LIFE TABLE, Louis I. Dublin, Alfred J. Lotka, and Mortimer Spiegelman, revised edition, The Ronald Press Co., New York, 1949, 379 pages, $7.00.

The striking improvement in the health and longevity of the American people in the fourteen years that have elapsed since the first edition was published has made the present revision necessary. Not only are the statistical tables brought up to date but it is in many ways a new book, which like its predecessor is an indispensable source for all physicians, biologists, sociologists, and welfare workers who are concerned with aging and old age. It should be carefully studied by those entering these fields and then kept close at hand for frequent reference.

The life table, carefully defined and its mathematical basis explained, serves to illustrate the historical progress toward increased longevity, the recent gains in the United States, and the biologic factors influencing longevity and mortality. The contribution of medical and sanitary science to health and longevity is reviewed in a compact well-written chapter. Longevity and mortality are analyzed in relation to physical condition and occupation. The applications of the life table to population problems and economic problems receive admirable study and analysis. The appendix contains a collection of life tables for this and other countries with the sources listed in a complete bibliography.

Physicians will be particularly interested in the authors' emphasis on the need for "long range studies of the prognosis in specific diseases and of the results of specific methods of treatment . . . . The contributions of life insurance companies cannot fully meet this need because of the limitations on the material available for their studies. Physicians, and especially those with a large hospital experience, are in the best position to carry on investigations of this kind because their patients are most likely to constitute a representative cross section of the experience of persons with a specific disease."

The Metropolitan Life Insurance Company may take just pride in the splendid work of its Statistical Department and its long record of public service under the leadership of Dr. Louis I. Dublin. Those of us who receive the monthly *Statistical Bulletin* are happy to acknowledge our debt to this great organization which generously shares its knowledge with us and endeavors in every way to further the cause of health education.

F. D. ZEMAN

BOOKS RECEIVED

Books received since November 1, 1949, are acknowledged in the following list. Insofar as space and time permit, some will be selected for review in a later issue, but it is unlikely that all will be reviewed.

Directory of Biological Laboratories, fourth edition, Burns Compiling & Research Organization, 200 Railway Exchange Bldg., Chicago, 1949, 140 pages, paper bound, $3.00. This is a list of laboratories in the United States concerned with biologic, bacteriologic, or biochemical investigations and includes the Equipment Annual & Materials Index.

Helpful Hints to the Diabetic, Charles C. Thomas, Publisher, Springfield, Illinois, 1949, 135 pages, $3.00.

Never Too Old, Legislative Document No. 32, New York State Joint Legislative Committee on Problems of the Aging, New York, 1949, 216 pages, paper bound; copies may be obtained free on request by writing to State Senator Thomas C. Desmond, 94 Broadway, Newburgh, New York.

Seelische Wandlungen beim alternden Menschen, Benno Schwabe & Co., Basel, 1949, 216 pages, $3.50. Copies may be ordered from Mr. A. J. Phiebig, Suite 906, 545 Fifth Ave., New York.

Selective Bibliography on the Welfare of Older People, Welfare Council of New York City, New York, 1949, 46 pages, paper bound, $1.00.

Social Welfare Forum, Proceedings of the National Conference of Social Work, 1949, Columbia University Press, New York, 1950, 312 pages, $4.25.

Social Work in the Current Scene, Selected Papers; National Conference of Social Work, 1949, Columbia University Press, New York, 1950, 392 pages, $4.75.

INDEX TO CURRENT PERIODICAL LITERATURE

NATHAN W. SHOCK
Section on Gerontology
National Heart Institute
National Institutes of Health

Beginning with the current issue, the Index to Current Periodical Literature will be classified to subject. The subject categories are those used in *A Bibliography of Gerontology and Geriatrics* by Nathan W. Shock to be published by Stanford University Press, Stanford, California. Only major headings will be used and the Roman numerals correspond to those given in the bibliography. In so far as possible, references are classified according to organ systems. Thus most of the material on Geriatrics will be found under the organ system involved in the disease. Cross references are indicated by number at the end of each section. When available abstract references are given (*B. A.* indicates Biological Abstracts and *P. A.* indicates Psychological Abstracts). Abbreviations for journals are those used in *A World List of Scientific Periodicals Published in the Years 1900-1933*, 2nd Edition. For journals not listed, abbreviations were devised according to the general rules used in the above source.

GERONTOLOGY

1. Clark, M.: Health in old age. Chap. 15, *in: Medicine on the March,* Funk & Wagnalls Co., N. Y., 1949, pp. 282-292.
2. Ferrannini, L.: *Una fiamma che resiste.* Centro di Medicina e Sociologia della Vecchiaia. G. Favia, Bari, 1948, 1-35 pp.
3. Korenchevsky, V.: The problem of ageing; basic difficulties of research. *Brit. med. J., 1:* 66-68, 1949. Abstr: *P. A., 23:* No. 5390, 1949.
4. O'Connor, W. A.: Definition of senility. *Brit. med. J., 2,* 1297, 1949.
5. Phillips, F.: The aging man in the modern world. *Med. J. Aust., 2:* 249-251, 1949.
6. Shock, N. W. (ed.): *Conference on problems of aging.* Josiah Macy, Jr. Foundation, N. Y., 1950, 258 pp.
7. Stieglitz, E. J.: The personal challenge of aging: biological changes and maintenance of health. Chap. 3, *in:* C. Tibbitts (ed.), *Living Through the Older Years,* Univ. Mich. Press, Ann Arbor, 1949, pp. 43-61.
8. Tibbitts, C. (ed.): *Living through the older years,* Univ. Mich. Press, Ann Arbor, 1949, 193 pp.
9. Weller, C. V.: Biologic aspects of the aging process. Chap. 2, *in:* C. Tibbitts, (ed.), *Living Through the Older Years,* Univ. Mich. Press, Ann Arbor, 1949, pp. 27-41.
10. Wilson, J. A.: Old Age. *Conn. St. med. J., 13:* 531-533, 1949.
11. Zeman, F. D.: The medical significance of our aging population. *Publ. Hlth. Nurs., 41:* 381-384, 1949.

BIOLOGY OF AGING

I. CELLULAR BIOLOGY AND PHYSIOLOGY
(includes plants)

12. Ashby, E.: Leaf shape and physiological age. *Endeavour, Lond., 8:* 18-25, 1949.
13. Ashby, E. and E. Wangermann: Senescence and rejuvenation in *Lemma minor. Nature, Lond., 164:* 187, 1949.

IV. LONGEVITY
(heredity, diet, occupation, sex differences)

14. Dickinson, F. G., and E. L. Welker: The leading causes of death among physicians. *J. Amer. med. Ass., 139:* 1129-1131, 1949.
15. Hays, F. A.: Sex influence on embryonic death rate in chicks. *Science, 110:* 533, 1949.
16. Hirsch, S.: La durée de la vie et le vieillissement de l'homme. De quelques aspects et buts de la gérontologie moderne. *Brux. méd., — :* (11), 1-22, March 1949.

IV-C LONGEVITY: *Comparative Physiology*

17. Melroy, M. B., and R. B. Spencer: Studies of survival of unicellular species. II. Some principles involved in the survival of bacterial species. *J. nat. Cancer Inst., 10:* 11-28, 1949.
18. Pemberton, C. E.: Longevity of the tropica' American toad, *Bufo marinus* L. *Science,* 512, 1949.
19. Spencer, R. R., and M. B. Melroy: survival of unicellular species.

in life expectancy of a paramecium under laboratory conditions. *J. nat. Cancer Inst., 10:* 1-10, 1949.

20. Wallerstein, R. S.: Longevity of *schistosoma mansoni;* observations based on a case. *Amer. J. trop. Med., 29:* 717-722, 1949.

See also Nos. 15, 282.

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XII. Reproductive System

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